

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 August 2003 (28.08.2003)

PCT

(10) International Publication Number
WO 03/070760 A2

(51) International Patent Classification⁷: **C07K 14/47**,
16/18, A61K 39/395, G01N 33/68

(21) International Application Number: PCT/EP03/01759

(22) International Filing Date: 20 February 2003 (20.02.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02003844.4 20 February 2002 (20.02.2002) EP

(71) Applicants (for all designated States except US): **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, CH-4070 Basel (CH). **MORPHOSYS AG** [DE/DE]; Lena-Christ-Strasse 48, 82152 Martinsried (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BARDROFF, Michael** [DE/DE]; Schietweg 2a, 81375 München (DE). **BOHRMANN, Bernd** [DE/DE]; Schlierbergstrasse 23, 79100 Freiburg (DE). **BROCKHAUS, Manfred** [DE/CH]; Talweg 29, CH-4126 Bettingen (CH). **HUBER, Walter** [CH/CH]; Ziegelhofweg 62, CH-4303 Kaiseraugst (CH). **KRETZSCHMAR, Titus** [DE/DE]; Pemmlerstrasse 10, 86857 Hurlach (DE). **LÖHNING, Corinna** [DE/DE]; Fleckhamerstrasse 12, 82131 Stockdorf (DE). **LOETSCHER, Hansruedi** [CH/CH]; Frankenstrasse

18, CH-4313 Möhlin (CH). **NORDSTEDT, Christer** [SE/SE]; Forskargatan 20, S-151 85 Sodertälje (SE). **ROTHER, Christine** [DE/DE]; Heinrich-Nicolausstrasse 26, 85221 Dachau (DE).

(74) Agent: **VOSSIUS & PARTNER**; Siebertstrasse 4, 81675 Munich (DE).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ANTI-A β ANTIBODIES AND THEIR USE

(57) Abstract: The present invention relates to antibody molecules capable of specifically recognizing two regions of the R-A4 peptide, wherein the first region comprises the amino acid sequence AEFRRHDSGY as shown in SEQ ID NO: 1 or a fragment thereof and wherein the second region comprises the amino acid sequence VHHQKLVFFAEDVG as shown in SEQ ID NO: 2 or a fragment thereof. Furthermore, nucleic acid molecules encoding the inventive antibody molecules and vectors and hosts comprising said nucleic acid molecules are disclosed. In addition, the present invention provides for compositions, preferably pharmaceutical or diagnostic compositions, comprising the compounds of the invention as well as for specific uses of the antibody molecules, nucleic acid molecules, vectors or hosts of the invention.



WO 03/070760 A2

Anti-A β antibodies and their use

The present invention relates to antibody molecules capable of specifically recognizing two regions of the β -A4 peptide, wherein the first region comprises the amino acid sequence AEFRHDSGY as shown in SEQ ID NO: 1 or a fragment thereof and wherein the second region comprises the amino acid sequence VHHQKLVFFAEDVG as shown in SEQ ID NO: 2 or a fragment thereof. Furthermore, nucleic acid molecules encoding the inventive antibody molecules and vectors and hosts comprising said nucleic acid molecules are disclosed. In addition, the present invention provides for compositions, preferably pharmaceutical or diagnostic compositions, comprising the compounds of the invention as well as for specific uses of the antibody molecules, nucleic acid molecules, vectors or hosts of the invention.

Several documents are cited throughout the text of this specification. Each of the documents cited herein (including any manufacturers specifications, instructions, etc.) are hereby incorporated by reference.

About 70% of all cases of dementia are due to Alzheimer's disease which is associated with selective damage of brain regions and neural circuits critical for cognition. Alzheimer's disease is characterized by neurofibrillary tangles in particular in pyramidal neurons of the hippocampus and numerous amyloid plaques containing mostly a dense core of amyloid deposits and defused halos.

The extracellular neuritic plaques contain large amounts of a pre-dominantly fibrillar peptide termed "amyloid β ", "A-beta", "A β 4", " β -A4" or "A β "; see Selkoe (1994), Ann. Rev. Cell Biol. 10, 373-403, Koo (1999), PNAS Vol. 96, pp. 9989-9990, US

4,666,829 or Glenner (1984), BBRC 12, 1131. This amyloid β is derived from "Alzheimer precursor protein/ β -amyloid precursor protein" (APP). APPs are integral membrane glycoproteins (see Sisodia (1992), PNAS Vol. 89, pp. 6075) and are endoproteolytically cleaved within the $A\beta$ sequence by a plasma membrane protease, α -secretase (see Sisodia (1992), loc. cit.). Furthermore, further secretase activity, in particular β -secretase and γ -secretase activity leads to the extracellular release of amyloid- β ($A\beta$) comprising either 39 amino acids ($A\beta_{39}$), 40 amino acids ($A\beta_{40}$), 42 amino acids ($A\beta_{42}$) or 43 amino acids ($A\beta_{43}$); see Sinha (1999), PNAS 96, 11094-1053; Price (1998), Science 282, 1078 to 1083; WO 00/72880 or Hardy (1997), TINS 20, 154.

It is of note that $A\beta$ has several naturally occurring forms, whereby the human forms are referred to as the above mentioned $A\beta_{39}$, $A\beta_{40}$, $A\beta_{41}$, $A\beta_{42}$ and $A\beta_{43}$. The most prominent form, $A\beta_{42}$, has the amino acid sequence (starting from the N-terminus): DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA (SEQ ID NO: 27). In $A\beta_{41}$, $A\beta_{40}$, $A\beta_{39}$, the C-terminal amino acids A, IA and VIA are missing, respectively. In the $A\beta_{43}$ -form an additional threonine residue is comprised at the C-terminus of the above depicted sequence (SEQ ID NO: 27).

The time required to nucleate $A\beta_{40}$ fibrils was shown to be significantly longer than that to nucleate $A\beta_{42}$ fibrils; see Koo, loc. cit. and Harper (1997), Ann. Rev. Biochem. 66, 385-407. As reviewed in Wagner (1999), J. Clin. Invest. 104, 1239-1332, the $A\beta_{42}$ is more frequently found associated with neuritic plaques and is considered to be more fibrillogenic in vitro. It was also suggested that $A\beta_{42}$ serves as a "seed" in the nucleation-dependent polymerization of ordered non-crystalline $A\beta$ peptides; Jarrett (1993), Cell 93, 1055-1058.

It has to be stressed that modified APP processing and/or the generation of extracellular plaques containing proteinaceous depositions are not only known from Alzheimer's pathology but also from subjects suffering from other neurological and/or neurodegenerative disorders. These disorders comprise, inter alia, Down's syndrome, Hereditary cerebral hemorrhage with amyloidosis Dutch type, Parkinson's

disease, ALS (amyotrophic lateral sclerosis), Creutzfeld Jacob disease, HIV-related dementia and motor neuropathy.

In order to prevent, treat and/or ameliorate disorders and/or diseases related to the pathological deposition of amyloid plaques, means and methods have to be developed which either interfere with β -amyloid plaque formation, which are capable of preventing A β aggregation and/or are useful in de-polymerization of already formed amyloid deposits or amyloid- β aggregates.

Accordingly, and considering the severe defects of modified and/or pathological amyloid biology, means and methods for treating amyloid related disorders are highly desirable. In particular, efficient drugs which either interfere with pathological amyloid aggregation or which are capable of de-polymerization of aggregated A β are desired. Furthermore, diagnostic means are desirable to detect, inter alia, amyloid plaques.

Thus, the technical problem of the present invention is to comply with the needs described herein above.

Accordingly, the present invention relates to an antibody molecule capable of specifically recognizing two regions of the β -A4/A β 4 peptide, wherein the first region comprises the amino acid sequence AEFRHDSGY (SEQ ID NO: 1) or a fragment thereof and wherein the second region comprises the amino acid sequence VHHQKLVFFAEDVG (SEQ ID NO: 2) or a fragment thereof.

In context of the present invention, the term "antibody molecule" relates to full immunoglobulin molecules, preferably IgMs, IgDs, IgEs, IgAs or IgGs, more preferably IgG1, IgG2a, IgG2b, IgG3 or IgG4 as well as to parts of such immunoglobulin molecules, like Fab-fragments or V_L-, V_H- or CDR-regions. Furthermore, the term relates to modified and/or altered antibody molecules, like chimeric and humanized antibodies. The term also relates to modified or altered monoclonal or polyclonal antibodies as well as to recombinantly or synthetically generated/synthesized antibodies. The term also relates to intact antibodies as well

as to antibody fragments/parts thereof, like, separated light and heavy chains, Fab, Fab/c, Fv, Fab', F(ab')₂. The term "antibody molecule" also comprises antibody derivatives, the bifunctional antibodies and antibody constructs, like single chain Fvs (scFv), bispecific scFvs or antibody-fusion proteins. Further details on the term "antibody molecule" of the invention are provided herein below.

The term "specifically recognizing" means in accordance with this invention that the antibody molecule is capable of specifically interacting with and/or binding to at least two amino acids of each of the two regions of β -A4 as defined herein. Said term relates to the specificity of the antibody molecule, i.e. to its ability to discriminate between the specific regions of the β -A4 peptide as defined herein and another, not related region of the β -A4 peptide or another, not APP-related protein/peptide/(unrelated) tests-peptide. Accordingly, specificity can be determined experimentally by methods known in the art and methods as disclosed and described herein. Such methods comprise, but are not limited to Western blots, ELISA-, RIA-, ECL-, IRMA-tests and peptide scans. Such methods also comprise the determination of K_D -values as, inter alia, illustrated in the appended examples. The peptide scan (pepspot assay) is routinely employed to map linear epitopes in a polypeptide antigen. The primary sequence of the polypeptide is synthesized successively on activated cellulose with peptides overlapping one another. The recognition of certain peptides by the antibody to be tested for its ability to detect or recognize a specific antigen/epitope is scored by routine colour development (secondary antibody with horseradish peroxidase and 4-chloronaphthol and hydrogenperoxide), by a chemoluminescence reaction or similar means known in the art. In the case of, inter alia, chemoluminescence reactions, the reaction can be quantified. If the antibody reacts with a certain set of overlapping peptides one can deduce the minimum sequence of amino acids that are necessary for reaction; see illustrative Example 6 and appended Table 2.

The same assay can reveal two distant clusters of reactive peptides, which indicate the recognition of a discontinuous, i. e. conformational epitope in the antigenic polypeptide (Geysen (1986), Mol. Immunol. 23, 709-715).

In addition to the pepspot assay, standard ELISA assay can be carried out. As demonstrated in the appended examples small hexapeptides may be coupled to a protein and coated to an immunoplate and reacted with antibodies to be tested. The scoring may be carried out by standard colour development (e.g. secondary antibody with horseradish peroxidase and tetramethyl benzidine with hydrogenperoxide). The reaction in certain wells is scored by the optical density, for example at 450 nm. Typical background (=negative reaction) may be 0.1 OD, typical positive reaction may be 1 OD. This means the difference (ratio) positive/negative can be more than 10 fold. Further details are given in the appended examples. Additional, quantitative methods for determining the specificity and the ability of "specifically recognizing" the herein defined two regions of the β -A4 peptide are given herein below.

The term "two regions of the β -A4 peptide" relates to two regions as defined by their amino acid sequences shown in SEQ ID NOs: 1 and 2, relating to the N-terminal amino acids 2 to 10 and to the central amino acids 12 to 25 of β -A4 peptide. The term " β -A4 peptide" in context of this invention relates to the herein above described A β 39, A β 41, A β 43, preferably to A β 40 and A β 42. A β 42 is also depicted in appended SEQ ID NO: 27. It is of note that the term "two regions of the β -A4 peptide" also relates to an "epitope" and/or an "antigenic determinant" which comprises the herein defined two regions of the β -A4 peptide or parts thereof. In accordance with this invention, said two regions of the β -A4 peptide are separated (on the level of the amino acid sequence) in the primary structure of the β -A4 peptide by at least one amino acid, preferably by at least two amino acids, more preferably by at least three amino acids, more preferably by at least four amino acids, more preferably by at least five amino acids, more preferably at least six amino acids, more preferably at least nine amino acids and most preferably at least twelve amino acids. As shown herein and as documented in the appended examples, the inventive antibodies/antibody molecules detect/interact with and/or bind to two regions of the β -A4 peptide as defined herein, whereby said two regions are separated (on the primary structure level of the amino acid sequence) by at least one amino acid and wherein the sequence separating said two regions/"epitope" may comprise more than ten amino acids, preferably 14 amino acids, more preferably 15 amino acids or

16 amino acids. For example, MSR-3 Fab (as an inventive antibody molecule) recognizes detects/interacts with two regions on the β -A4 peptide, wherein said first region comprises amino acids 3 and 4 (EF) and said second regions comprises amino acids 18 to 23 (VFFAED). Accordingly, the separating sequence between the region/epitopes to be detected/recognized has a length of 13 amino acids on the primary amino acid sequence structure. Similarly, MSR #3.4H7 IgG1, an optimized and matured antibody molecules derived from MSR-3 and comprised in an IgG1-framework, detects/interacts with/binds to two epitopes/regions of β -A4 which comprise in the first region positions 1 to 4 (DAEF) and in the second region positions 19 to 24 (FFAEDV) of β -A4 as defined herein. Accordingly, MSR #3.4H7 IgG1 recognizes/detects/interacts with/binds to two epitopes/regions which are, on the primary amino acid sequence level, separated by 14 amino acids. As detailed in the appended examples, affinity maturation and conversion of monovalent inventive Fab fragments to full-length IgG1 antibodies may result in a certain broadening of the epitopes/regions detected in pepspot, ELISA assays and the like. Therefore, the antibody molecules of the invention are capable of simultaneously and independently recognizing two regions of the β -A4 peptide/A β 4 wherein said regions comprise the amino acid sequence as shown in SEQ ID NO: 1 (or parts thereof) and the amino acid sequence as shown in SEQ ID NO: 2 (or (a) part(s) thereof). Due to the potential broadening of epitopes as detailed herein it is, however, also envisaged that amino acids in close proximity to the sequences of SEQ ID NO: 1 and 2 are detected/recognized, i.e. that additional amino acids are part of the two regions to be detected/recognized. Accordingly, it is also envisaged that, e.g. the first amino acid of A β (1-42) as defined herein, namely D (Aspartic acid) in part of one epitope to be detected/recognized or that amino acids located after the region of A β (1-42) as defined in SEQ ID NO: 2 are detected/recognized. Said additional amino acid may, e.g., be the amino acid on position 26 of SEQ ID NO: 27 (β A4/A β (1-42)), namely S (Serine).

The term may also relate to a conformational epitope, a structural epitope or a discontinuous epitope consisting of said two regions or parts thereof; see also Geysen (1986), loc. cit. In context of this invention, a conformational epitope is defined by two or more discrete amino acid sequences separated in the primary

sequence which come together on the surface when the polypeptide folds to the native protein (Sela, (1969) Science 166, 1365 and Laver, (1990) Cell **61**, 553-6). The antibody molecules of the present invention are envisaged to specifically bind to/interact with a conformational/structural epitope(s) composed of and/or comprising the two regions of β -A4 described herein or parts thereof as disclosed herein below. The "antibody molecules" of the present invention are thought to comprise a simultaneous and independent dual specificity to (a) an amino acid stretch comprising amino acids 2 to 10 (or (a) part(s) thereof) of β -A4 and (b) an amino acid stretch comprising amino acids 12 to 25 (or (a) part(s) thereof) of β -A4 (SEQ ID NO. 27). Fragments or parts of these stretches comprise at least two, more preferably at least three amino acids. Preferred fragments or parts are in the first region/stretch of SEQ ID NO: 27 the amino acid sequences AEFRHD, EF, EFR, FR, EFRHDSG, EFRHD or HDSG and in the second region/stretch of SEQ ID NO: 27 the amino acid sequences HHQKL, LV, LVFFAE, VFFAED VFFA, or FFAEDV. As mentioned above, said fragments may also comprise additional amino acids or may be parts of the fragments defined herein. Specific examples are DAE, DAEF, FRH or RHDSG.

A number of antibodies specifically recognizing A β peptides have been described in the art. These antibodies have mainly been obtained by immunizing animals with A β 1-40 or A β 1-42 or fragments thereof using standard technologies. According to published data monoclonal antibodies that were generated by immunization with the complete A β peptide (1-40 or 1-42) recognize exclusively an epitope close to the N-terminus of A β . Further, examples are the antibodies BAP-1 and BAP-2 (Brockhaus, unpublished) which were generated by immunization of mice with A β 1-40 and which recognize the amino acids 4-6 in the context of larger A β peptides; see appended Example 7, Table 2 and Example 12, Table 7. Antibodies that recognize the middle part of A β derive from immunizations with smaller peptides. For example, the antibody 4G8 was generated by immunization with the A β peptide 1-24 and recognizes exclusively the sequence 17-24 (Kim, (1988) Neuroscience Research Communications 2, 121-130). Many other monoclonal antibodies have been generated by immunizing mice with A β -derived fragments, and antibodies recognizing the C-terminal end of A β 1-40 and A β 1-42 are widely used to distinguish

and quantitate the corresponding A β peptides in biological fluids and tissues by ELISA, Western blot and immunohistochemistry analysis (Ida et al, (1996) J. Biol. Chem. 271, 22908-22914; Johnson-Wood et al., (1997), Proc. Natl. Acad. Sci. USA (1994), 1550-1555; Suzuki et al., (1994), Science 264, 1336-1340; Brockhaus (1998), Neuro Rep. 9, 1481-1486). BAP-17 is a mouse monoclonal antibody which has been generated by immunizing mice with A β fragment 35-40. It specifically recognizes the C-terminal end of A β 1-40 (Brockhaus (1998) Neuroreport 9, 1481-1486).

It is believed that the immunization with T-cell dependent antigens (often poor immunogens) requires a proteolytic cleavage of the antigen in the endosomes of antigen presenting cells. The in vivo selection of high affinity antibodies after immunization is driven by the contact of helper T cells to antigen presenting cells. The antigen presenting cells only present short peptides and not polypeptides of large size. Accordingly, these cells have a complicated (but well known) machinery to endocytose antigen(s), degrade the antigen(s) in endosomes, combine selected peptides with suitable MHC class II molecules, and to export the peptide-MHC complex to the cell surface. This is where the antigen specific recognition by T cells occurs, with the aim to provide help to maturing B cells. The B cells which receive most T cell help have the best chance to develop into antibody secreting cells and to proliferate. This shows that antigen processing by proteolysis is an important step for the generation of an high affinity antibody response in vivo and may explain the dominance of the N-terminal A β epitope in prior art monoclonal and polyclonal antibodies derived by immunization.

In contrast, the selection of antibodies/antibody molecules of the present invention is driven by the physical adherence of Fab expressing phages to the antigen. There is no degradation of the antigen involved in this in vitro selection process. The phages which express the Fab with the highest affinity towards the antigen are selected and propagated. A synthetic library as employed in the appended examples to select for specific antibody molecules according to this invention is particularly suited for avoiding any bias for single, continuous epitopes that is often found in libraries derived from immunized B cells.

It is of note that the prior art has not described antibody molecules recognizing two, independent regions of A β 4 which specifically recognizes (a) discontinuous/structural/conformational epitope(s) and/or which are capable of simultaneously and independently recognizing two regions/epitopes of A β 4.

Vaccination of transgenic mice overexpressing mutant human APP_{V717F} (PDAPP mice) with A β 1-42 resulted in an almost complete prevention of amyloid deposition in the brain when treatment was initiated in young animals, i. e. before the onset of neuropathologies, whereas in older animals a reduction of already formed plaques was observed suggesting antibody-mediated clearance of plaques (Schenk et al., (1999), Nature 400,173-177). The antibodies generated by this immunization procedure were reactive against the N-terminus of A β 4 covering an epitope around amino acids 3-7 (Schenk et al., (1999), loc. cit.; WO 00/72880). Active immunization with A β 1-42 also reduced behavioural impairment and memory loss in different transgenic models for Alzheimer's Disease (Janus et al., (2000) Nature 408, 979-982; Morgan et al., (2000) Nature 408, 982-985). Subsequent studies with peripherally administered antibodies, i. e. passive immunization, have confirmed that antibodies can enter the central nervous system, decorate plaques and induce clearance of preexisting amyloid plaques in APP transgenic mice (PDAPP mice) (Bard et al., (2000) Nat. Med. 6, 916-919; WO 00/72880). In these studies, the monoclonal antibodies with the most potent *in vivo* and *ex vivo* efficacy (triggering of phagocytosis in exogenous microglial cells) were those which recognized A β 4 N-terminal epitopes 1-5 (mab 3D6, IgG2b) or 3-6 (mab 10D5, IgG1). Likewise, polyclonal antibodies isolated from mice, rabbits or monkeys after immunization with A β 1-42 displayed a similar N-terminal epitope specificity and were also efficacious in triggering phagocytosis and *in vivo* plaque clearing. In contrast, C-terminal specific antibodies binding to A β 1-40 or A β 1-42 with high affinity did not induce phagocytosis in the *ex vivo* assay and were not efficacious *in vivo* (WO 00/72880). Monoclonal antibody m266 (WO 00/72880) was raised against A β 13-28 (central domain of A β) and epitope mapping confirmed the antibody specificity to cover amino acids 16-24 in the A β sequence. This antibody does not bind well to aggregated A β and amyloid deposits and merely reacts with soluble (monomeric) A β , i. e. properties which are similar to another well-known and commercially available monoclonal antibody (4G8;

Kim, (1988) Neuroscience Research Communications 2, 121-130; commercially available from Signet Laboratories Inc. Dedham, MA USA) which recognizes the same epitope.

In vivo, the m266 antibody was recently found to markedly reduce A β deposition in PDAPP mice after peripheral administration (DeMattos, (2001) Proc. Natl. Acad. Sci. USA 98, 8850-8855). However, and in contrast to N-terminal specific antibodies, m266 did not decorate amyloid plaques *in vivo*, and it was therefore hypothesized that the brain A β burden was reduced by an antibody-induced shift in equilibrium between CNS and plasma A β resulting in the accumulation of brain-derived A β in the periphery, firmly complexed to m266 (DeMattos, (2001) loc. cit.).

The antibodies/antibody molecules of the present invention, by simultaneously (for example in a structural/conformational epitope formed by the N-terminal and central region of β A4 as described herein) and independently (for example in pepspot assays as documented in the appended experimental part) binding to the N-terminal and central epitopes, combine the properties of an N-terminal-specific antibody and a central epitope-specific antibody in a single molecule. Antibodies with the dual epitope specificity, as described in the present invention, are considered to be more efficacious *in vivo*, in particular in medical and diagnostic settings for, e.g., reducing amyloid plaque burden or amyloidogenesis or for the detection of amyloid deposits and plaques. It is well known that in the process of A β 4 aggregation and amyloid deposition conformational changes occur, and while the central epitope is easily accessible in soluble A β 4 it appears to be hidden and less reactive in aggregated or fibrillar A β 4. The fact that the central/middle epitope-specific antibody m266 is efficacious *in vivo* indicates that neutralization of soluble A β 4 may also be a critical parameter. The antibodies/antibody molecules of the present invention, due to the dual epitope specificity, can bind to both fibrillar and soluble A β 4 with similar efficacy, thus allowing interaction with amyloid plaques as well as neutralization of soluble A β 4. The term "simultaneously and independently binding to the N-terminal and central/middle epitopes of β -A4" as employed herein in context of the inventive antibody molecules relates to the fact that the antibodies/antibody molecules

described herein may detect and/or bind to both epitopes simultaneously, i.e. at the same time (for example on conformational/structural epitopes formed by the N-terminal epitope (or (a) part(s) thereof) and central epitopes (or (a) part(s) thereof) of β A4 as defined herein) and that the same antibody molecules, however, are also capable of detecting/binding to each of the defined epitopes in an independent fashion, as inter alia, demonstrated in the pepspot analysis shown in the examples.

Clearance of amyloid plaques *in vivo* in PDAPP mice after direct application of the antibodies to the brain is not dependent on the IgG subtype and may also involve a mechanism which is not Fc-mediated, i. e. no involvement of activated microglia in plaque clearance (Bacsikai, (2001), Abstract Society for Neuroscience 31st Annual Meeting, November 10-15, 2001, San Diego). This observation is in contrast to what has been postulated in an earlier study by Bard (2000), loc. cit.

In another study antibodies raised against $A\beta$ 1-28 and $A\beta$ 1-16 peptides were found to be effective in disaggregating $A\beta$ fibrils *in vitro*, whereas an antibody specific for $A\beta$ 13-28 was much less active in this assay (Solomon, (1997) Proc. Natl. Acad. Sci. USA 94, 4109-4112). Prevention of $A\beta$ aggregation by an anti- $A\beta$ 1-28 antibody (AMY-33) has also been reported (Solomon, (1996) Proc. Natl. Acad. Sci. USA 93, 452-455). In the same study, antibody 6F/3D which has been raised against $A\beta$ fragment 8-17 slightly interfered with Zn^{2+} -induced $A\beta$ aggregation but had no effect on the self aggregation induced by other aggregation-inducing agents.

The efficacy of the various antibodies in these *in vitro* assays correlates with the accessibility of their epitopes in $A\beta$ 4 aggregates. The N-terminus is exposed and N-terminal specific antibodies clearly induce de-polymerization, whereas the central region and the C-terminus are hidden and not easily accessible and thus antibodies against these epitope are much less effective.

Investigations with respect to epitope accessibility for antibodies have shown that in aggregated $A\beta$ the N-terminal epitope is exposed and reacts with the BAP-1 antibody, whereas the middle or central epitope indeed remains cryptic, i. e. no binding of the 4G8 antibody was observed. However, in monomeric $A\beta$ both epitopes are overt and are equally recognized by both prior art antibodies.

In contrast, in the present invention, it was surprisingly found that the herein described antibody molecules recognize two discontinuous amino acid sequences, e.g. a conformational/structural epitope on the A β peptide. Two "discontinuous amino acid sequences" in accordance with this invention means that said two amino acid sequences forming the N-terminal and central/middle epitopes, respectively, are separated on β -A4 in its primary structure by at least two amino acids which are not part of either epitope.

The binding area of an antibody Fab (=paratope) occupies a molecular surface of approximately 30 x 30 Å in size (Laver, Cell 61 (1990), 553-556). This is enough to contact 15 to 22 amino acid residues which may be present on several surface loops. The discontinuous epitope recognized by the inventive antibody molecules resembles a conformation in which the N-terminal (residues 2 to 10 or parts thereof) and middle A β peptide sequences (residues 12 to 25 or parts thereof) are in close proximity. Only within this conformation, the maximum number of antigen-antibody contacts and the lowest free energy state are obtained.

Based on energetic calculations it has been suggested that a smaller subset of 5-6 residues, which are not arranged in a linear sequence but are scattered over the epitope surface, contributes most of the binding energy while surrounding residues may merely constitute a complementary array (Laver (1990) loc. cit.).

The inventive antibodies/antibody molecules are capable of binding to aggregated A β and strongly react with amyloid plaques in the brain of AD patients (as documented in the appended examples). In addition, they are capable of de-polymerizing/disintegrating amyloid aggregates.

Without being bound by theory, the conformational/structural epitope (composed by the two regions of A β 4 or (a) part(s) of said regions as described herein) is believed to be partially exposed in aggregated A β . However, it is known that major part of the middle/second epitope/region alone is not freely accessible in these A β aggregates (based on the poor reactivities of middle epitope-specific antibodies 4G8 and m266). On the other hand, and in view of the considerations mentioned above, it is likely

that one or several residues of the middle region are components of the conformational epitope and, in conjunction with the residues from the N-terminal region, are accessible to the antibodies of the present invention, thereby significantly contributing to the binding energy of the antibody-A β 4 interaction. The reactivity of the inventive antibody molecules with the conformational epitope in aggregated A β is therefore unique and clearly distinct from α -A β 4 antibodies described in the prior art. Yet, as pointed out herein above, a further unique feature of the inventive antibodies/antibody molecules is their capacity to simultaneously and independently binding to/recognizing two separate epitopes on β -A4, as defined herein and in the appended examples.

In a preferred embodiment of the invention, the inventive antibody molecule is an antibody molecule wherein the least two regions of the β -A4 to be specifically recognized by said antibody form a conformational/structural epitope or a discontinuous epitope; see Geysen (1986), loc. cit.; Ghoshal (2001), J. Neurochem. 77, 1372-1385; Hochleitner (2000), J. Imm. 164, 4156-4161; Laver (1990), loc. cit.. The term "discontinuous epitope" means in context of the invention non-linear epitopes that are assembled from residues from distant portions of the polypeptide chain. These residues come together on the surface when the polypeptide chain folds into a three-dimensional structure to constitute a conformational/structural epitope. The present invention provides for preferred, unexpected epitopes within β -A4, which result in the inventive generation of specific antibody molecules, capable of specifically interacting with these epitopes. These inventive antibodies/antibody molecules provide the basis for increased efficacy, and a reduced potential for side effects. As pointed out above, the inventive antibodies, however, were also capable of independently interacting with each of the defined two regions/epitopes of β -A4, for example in Pepspot assays as documented in the appended examples.

The present invention, accordingly, provides for unique tools which may be employed to de-polymerize aggregated A β -fibrils in vivo and in vitro and/or which are capable of stabilizing and/or neutralizing a conformational epitope of monomeric A β and thereby capable of preventing the pathological A β aggregation.

It is furthermore envisaged that the inventive antibodies bind to A β deposits at the rim of amyloid plaques in, inter alia, Alzheimer's brain and efficiently dissolve the pathological protofibrils and fibrils.

In a preferred embodiment, the antibody molecule of the invention recognizes at least two consecutive amino acids within the two regions of A β 4 defined herein, more preferably said antibody molecule recognizes in the first region an amino acid sequence comprising the amino acids: AEFRHD, EF, EFR, FR, EFRHDSG, EFRHD or HDSG and in the second region an amino acid sequence comprising the amino acids: HHQKL, LV, LVFFAE, VFFAED, VFFA or FFAEDV. Further fragments or broadened parts comprise: DAE, DAEF, FRH or RHDSG.

It is particularly preferred that the antibody molecule of the invention comprises a variable V_H-region as encoded by a nucleic acid molecule as shown in SEQ ID NO: 3, 5 or 7 or a variable V_H-region as shown in the amino acid sequences depicted in SEQ ID NOs: 4, 6 or 8. The sequences as shown in SEQ ID NOs: 3 and 4 depict the coding region and the amino acid sequence, respectively, of the V_H-region of the inventive, parental antibody MSR-3 (MS-Roche 3), the sequences in SEQ ID NOs: 5 and 6 depict the coding region and the amino acid sequence, respectively, of the V_H-region of the inventive, parental antibody MSR-7 (MS-Roche 7) and SEQ ID NOs: 7 and 8 depict the coding region and the amino acid sequence, respectively, of the V_H-region of the inventive, parental antibody MSR-8 (MS-Roche 8). Accordingly, the invention also provides for antibody molecules which comprise a variable V_L-region as encoded by a nucleic acid molecule as shown in a SEQ ID NO selected from the group consisting of SEQ ID NO: 9, 11 or 13 or a variable V_L-region as shown in the amino acid sequences depicted in SEQ ID NOs: 10, 12 or 14. SEQ ID NOs: 9 and 10 correspond to the V_L-region of MSR-3, SEQ ID NOs: 11 and 12 correspond to the V_L-region of MSR-7 and SEQ ID NOs: 13 and 14 correspond to the V_L-region of MSR-8. As illustrated in the appended examples, the parental antibodies MSR-3, -7 and -8, are employed to further generate optimized antibody molecules with even better properties and/or binding affinities. Some of the corresponding and possible strategies are exemplified and shown in the appended examples.

The optimization strategy as illustrated in the appended examples lead to a plurality of inventive, optimized antibodies. These optimized antibodies share with their parental antibodies the CDR-3 domain of the V_H -region. Whereas the original framework region (as shown in appended Figure 1) remains the same, in the matured/optimized antibody molecules, CDR1, CDR2 and/or V_L CDR3-regions are changed. Illustrative, modified sequence motives for optimized antibody molecules are shown in appended table 1. Accordingly, within the scope of the present invention are also optimized antibody molecules which are derived from the herein disclosed MSR-3, -7 and -8 and which are capable of specifically reacting with/specifically recognizing the two regions of the β -A4 peptide as defined herein. In particular, CDR-regions, preferably CDR1s, more preferably CDR1s and CDR2s, most preferably CDR1s, CDR2s and CDR3s as defined herein may be employed to generate further inventive antibodies/antibody molecules, inter alia, by CDR-grafting methods known in the art; see Jones (1986), Nature 321, 522-515 or Riechmann (1988), Nature 332, 323-327. Most preferably the inventive antibodies/antibody molecules as well as antibody fragments or derivatives are derived from the parental antibodies as disclosed herein and share, as disclosed above, the CDR-3 domain of the V_H -region with at least one of said parental antibodies. As illustrated below, it is also envisaged that cross-cloned antibodies are generated which are to be considered as optimized/matured antibodies/antibody molecules of the present invention. Accordingly, preferred antibody molecules may also comprise or may also be derived from antibodies/antibody molecules which are characterized by V_H -regions as shown in any of SEQ ID NOs: 32 to 45 or V_L -regions as shown in SEQ ID NOs: 46 to 59 or which may comprise a CDR-3 region as defined in any of SEQ ID NOs: 60 to 87. In a particular preferred embodiment, the optimized antibody molecule of the present invention comprises V_H -regions and V_L -regions as depicted in SEQ ID NOs: 88/89 and 90/91, respectively, or parts thereof. Apart thereof may be (a) CDR-region(s), preferably (a) CDR3-region(s). A particularly preferred antibody molecule of the optimized type comprises a H-CDR3 as characterized in SEQ ID NOs: 92 or 93 and/or a L-CDR3 as characterized in SEQ ID NOs: 94 or 95. It is preferred that the antibodies/antibody molecules of the invention are characterized by their specific reactivity with β -A4 and/or peptides derived from said β -A4. For example, optical densities in ELISA-tests, as illustrated in the appended

examples, may be established and the ratio of optical densities may be employed to define the specific reactivity of the parental or the optimized antibodies. Accordingly, a preferred antibody of the invention is an antibody which reacts in an ELISA-test with β -A4 to arrive at an optical density measured at 450 nm that is 10 times higher than the optical density measured without β -A4, i. e. 10 times over background. Preferably the measurement of the optical density is performed a few minutes (e.g. 1, 2, 3, 4, 5, 6, or 7 minutes) after initiation of the color developing reaction in order to optimize signal to background ratio.

In a particular preferred embodiment, the inventive antibody molecule comprises at least one CDR3 of an V_L -region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 15, 17 or 19 or at least one CDR3 amino acid sequence of an V_L -region as shown in SEQ ID NOs: 16, 18 or 20 and/or said antibody molecule comprises at least one CDR3 of an V_H -region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 21, 23 or 25 or at least one CDR3 amino acid sequence of an V_H -region as shown in SEQ ID NOs: 22, 24 or 26. Most preferred are antibodies comprising at least one CDR3 of an V_H -region as defined herein. The CDR-3 domains mentioned herein above relate to the inventive, illustrative parental antibody molecules MSR-3, -7, or -8. However, as illustrated in the appended tables 1, 8 or 10, matured and/or optimized antibody molecules obtainable by the methods disclosed in the appended examples may comprise modified V_H -, V_L -, CDR1, CDR2 and CDR3 regions. Accordingly, the antibody molecule of the invention is preferably selected from the group consisting of MSR-3, -7 and -8 or an affinity-matured version of MSR-3, -7 or -8. Affinity-matured as well as cross-cloned versions of MSR-3, -7 and -8 comprise, inter alia, antibody molecules comprising CDR1, CDR2 and/or CDR3 regions as shown in table 1 or 8 or characterized in any of SEQ ID NOs: 15 to 20, 21 to 26, 60 to 74, 75 to 87, 92 and 93 or 94 and 95 as well as in SEQ ID NOs: 354 to 413. Most preferably, the antibody of the invention comprises at least one CDR, preferably a CDR1, more preferably a CDR2, most preferably a CDR3 as shown in the appended table 1, 8 or as documented in appended table 10.

It is of note that affinity-maturation techniques are known in the art, described in the appended examples and, inter alia, in Knappik (2000), J. Mol. Biol. 296, 55; Krebs

(2000), J. Imm. Meth. 254, 67-84; WO 01/87337; WO 01/87338; US 6,300,064; EP 96 92 92 78.8 and further references cited herein below.

In a more preferred embodiment of the invention, the antibody molecule is a full antibody (immunoglobulin, like an IgG1, an IgG2, an IgG2b, an IgG3, an IgG4, an IgA, an IgM, an IgD or an IgE), an F(ab)-, Fabc-, Fv-, Fab'-, F(ab')₂- fragment, a single-chain antibody, a chimeric antibody, a CDR-grafted antibody, a bivalent antibody-construct, an antibody-fusion protein, a cross-cloned antibody or a synthetic antibody. Also envisaged are genetic variants of immunoglobulin genes. Genetic variants of, e.g., immunoglobulin heavy G chain subclass 1 (IgG1) may comprise the G1m(17) or G1m(3) allotypic markers in the CH1 domain, or the G1m(1) or the G1m(non-1) allotypic marker in the CH3 domain. The antibody molecule of the invention also comprises modified or mutant antibodies, like mutant IgG with enhanced or attenuated Fc-receptor binding or complement activation. It is also envisaged that the antibodies of the invention are produced by conventional means, e.g. the production of specific monoclonal antibodies generated by immunization of mammals, preferably mice, with peptides comprising the two regions of β A4 as defined herein, e.g. the N-terminal and central region/epitope comprising (a) amino acids 2 to 10 (or (a) part(s) thereof) of β -A4 and (b) an amino acid stretch comprising amino acids 12 to 25 (or (a) part(s) thereof) of β -A4 (SEQ ID NO. 27). Accordingly, the person skilled in the art may generate monoclonal antibodies against such a peptide and may screen the obtained antibodies for the capacity to simultaneously and independently binding to/reacting with the N-terminal and central region/epitope of β A4 as defined herein. Corresponding screening methods are disclosed in the appended examples.

As illustrated in the appended examples, the inventive antibodies/antibody molecules can readily and preferably be recombinantly constructed and expressed. Preferably, the antibody molecule of the invention comprises at least one, more preferably at least two, preferably at least three, more preferably at least four, more preferably at least five and most preferably six CDRs of the herein defined MSR-3, MSR-7 or MSR-8 parental antibodies or of affinity-matured/optimized antibodies derived from said parental antibodies. It is of note that also more than six CDRs may

be comprised in recombinantly produced antibodies of the invention. The person skilled in the art can readily employ the information given in the appended examples to deduce corresponding CDRs of the parental as well as the affinity optimized antibodies. Examples of optimized antibodies which have been obtained by maturation/optimization of the parental antibodies are, inter alia, shown in appended table 1. An matured/optimized antibody molecule of the invention is, e.g. MSR 7.9H7 which is also characterized by sequences appended herein, which comprise SEQ ID NOs: 88 to 95 and which depict the V_H-region of MSR 7.9H7 (SEQ ID NOs: 88 and 89), the V_L-region of MSR 7.9H7 (SEQ ID NOs: 90 and 91), the H-CDR3 of MSR 7.9H7 (SEQ ID NOs: 92 and 93) as well as the L-CDR3 of MSR 7.9H7 (SEQ ID NOs: 94 and 95). Illustrative antibody molecule 7.9H7 is derived from parental antibody MSR7 and is a particular preferred inventive example of an optimized/matured antibody molecule of the present invention. This antibody molecule may be further modified in accordance with this invention, for example in form of cross-cloning, see herein below and appended examples.

As documented in the appended examples, the antibodies of the invention also comprise cross-cloned antibodies, i.e. antibodies comprising different antibody regions (e.g. CDR-regions) from one or more parental or affinity-optimized antibody(ies) as described herein. These cross-cloned antibodies may be antibodies in several, different frameworks, whereby the most preferred framework is an IgG-framework, even more preferred in an IgG1-, IgG2a or an IgG2b-framework. It is particularly preferred that said antibody framework is a mammalian, most preferably a human framework. The domains on the light and heavy chains have the same general structure and each domain comprises four framework regions, whose sequences are relatively conserved, joined by three hypervariable domains known as complementarity determining regions (CDR1-3).

As used herein, a "human framework region" relates to a framework region that is substantially identical (about 85% or more, usually 90-95% or more) to the framework region of a naturally occurring human immunoglobulin. The framework region of an antibody, that is the combined framework regions of the constituent light and heavy chains, serves to position and align the CDR's. The CDR's are primarily

responsible for binding to an epitope of an antigen. It is of note that not only cross-cloned antibodies described herein may be presented in a preferred (human) antibody framework, but also antibody molecules comprising CDRs from, inter alia, the parental antibodies MSR-3, -7 or -8 as described herein or of matured antibodies derived from said parental antibodies, may be introduced in an immunoglobulin framework. Preferred frameworks are IgG1, IgG2a and IgG2b. Most preferred are human frameworks and human IgG1 frameworks.

As shown in the appended examples, it is, inter alia possible, to transfer, by genetic engineering known in the art whole light chains from an optimized donor clone to an optimized recipient clone. Example for an optimized donor clone is, e.g. L-CDR1 (L1) and an example for an optimized recipient clone is H-CDR2 (H2). Epitope specificity may be conserved by combining clones which possess the same H-CDR-3 regions. Further details are given in illustrative Example 13.

Preferred cross-cloned antibody molecules of the invention are selected from the group consisting of MS-R #3.3H1x3.4L9, MS-R #3.4H1x3.4L9, MS-R #3.4H3x3.4L7, MS-R #3.4H3x3.4L9, MS-R #3.4H7x3.4L9, MS-R #3.4H7x3.4L7, MS-R #3.6H5x3.6L1, MS-R #3.6H5x3.6L2, MS-R #3.6H8x3.6L2, MS-R #7.2H2x7.2L1, MS-R #7.4H2x7.2L1, MS-R #7.4H2x7.12L2, MS-R #7.9H2x7.2L1(L1), MS-R #7.9H2x7.12L1, MS-R #7.9H2x7.12L2, MS-R #7.9H2x7.12L2(L1+2), MS-R #7.9H4x7.12L2, MS-R #7.11H1x7.2L1, MS-R #7.11H1x7.11L1, MS-R #7.11H2x7.2L1(L1), MS-R #7.11H2x7.9L1 (L1), MS-R #7.11H2x7.12L1 or MS-R #8.1H1x8.2L1.

The generation of cross-cloned antibodies is also illustrated in the appended examples. The above mentioned preferred cross-cloned antibodies/antibody molecules are optimized/matured antibody molecules derived from parental antibodies disclosed herein, in particular from MSR-3 and MSR-7. In addition, further characterizing CDR-sequences and V-regions of the cross-cloned antibody molecules/antibodies are given in appended SEQ ID NOs: 32, 33, 46 and 47 (MSR 3.6H5x3.6L2; V_H-, V_L-region); 34, 35, 48 and 49 (MSR 3.6H8x3.6L2; V_H-, V_L-regions); 36, 37, 50 and 51 (MSR 7.4H2x7.2L1; V_H-, V_L-regions); 38, 39, 52 and 53 (MSR 7.9H2x7.12L2; V_H-, V_L-regions); 40, 41, 54 and 55 (MSR # 7.9H4x7.12L2;

V_H-, V_L-regions); 42, 43, 56 and 57 (MSR #7.11H1x7.11.L1; V_H-, V_L-regions); and 44, 45, 58 and 59 (MSR # 7.11H1x7.2.L1; V_H-, V_L-regions). Corresponding CDR3 regions of these particular preferred cross-cloned antibody molecules are depicted in SEQ ID NOs: 60 to 87. For further MSR antibody molecules, V_H-, V_L-, CDR-regions can be deduced from appended Tables 8 or 10 and from the appended sequence listing, in particular SEQ ID NOS: 32 to 95 for MS-R antibodies/antibody molecules #3.6H5 x 3.6L2, #3.6H8 x 3.6L2, #7.4H2 x 7.2L1, #7.9H2 x 7.12L2, #7.9H4 x 7.12L2, #7.11H1 x 7.11L1, #7.11H1 x 7.2L1 and #7.9H7 or SEQ ID NOS: 294 to 413 for MSR-R antibodies/antibody molecules MS-R #3.3H1x3.4L9, #3.4H1 x 3.4L9, #3.4H3 x 3.4L7, #3.4H3 x 3.4L9, #3.4H7 x 3.4L9, #3.4H7 x 3.4L7, #3.6H5 x 3.6L1, #7.2H2 x 7.2L1, #7.4H2 x 7.12L2, #7.9H2 x 7.2L1, #7.9H2 x 7.12L1, #7.11H2 x 7.2L1, #7.11H2 x 7.9L1, #7.11H2 x 7.12L1 or #8.1H1 x 8.2L1. Accordingly, besides V_H-regions defined above, preferred antibody molecules of the invention may comprise V_H-regions as defined in any one of SEQ ID NOs: 294 to 323. Similarly, SEQ ID NOs: 324 to 353 depict preferred V_L-regions which, besides to V_L-regions defined above which may be comprised in the inventive antibody molecules. Corresponding CDR-3 regions are defined above, as well as in additional sequences shown in SEQ ID NOs: 354 to 413.

Inventive antibody molecules can easily be produced in sufficient quantities, inter alia, by recombinant methods known in the art, see, e.g. Bentley, *Hybridoma* 17 (1998), 559-567; Racher, *Appl. Microbiol. Biotechnol.* 40 (1994), 851-856; Samuelsson, *Eur. J. Immunol.* 26 (1996), 3029-3034.

Theoretically, in soluble β -A4 (monomeric/oligomeric) both the N-terminal and the middle epitopes are accessible for antibody interaction and antibody molecules of the present invention may either bind to the N-terminal or middle epitope separately, but under these conditions maximum affinity will not be obtained. However, it is more likely that an optimal contact to the antibody paratope will be attained by simultaneous binding to both epitopes, i.e. similar to the interaction with aggregated β -A4. Thus, antibodies of the present invention are unique anti-A β antibodies in that they bind to aggregated β -A4 (via interaction with the N-terminal and middle epitope), and at the same time are also able to stabilize and neutralize the

conformational epitope in soluble β -A4. These antibodies are distinct to prior art antibodies.

Most preferred are antibody molecules of the invention which have an affinity to A β or defined fragments thereof with a K_D value lower than 2000 nM, preferably lower than 100 nM, more preferably lower than 10 nM, most preferably lower than 1 nM. The measurement of such affinity/affinities may be carried out by methods illustrated in the examples and known in the art. Such methods comprise, but are not limited to BIACORETM-assays (www.biacore.com; Malmquist (1999), Biochem.Soc. Trans 27, 335-340) and solid phase assays using labeled antibodies or labeled A β .

Preferably, the antibody molecule of the invention is capable of decorating/reacting with/binding to amyloid plaques in in vitro (post-mortem) brain sections from patients suffering from amyloid-related disorders, like Alzheimer's disease. Yet, it is also preferred that the inventive antibody/antibody molecules prevent A β -aggregation in vivo as well as in in vitro assays, as illustrated in the appended examples. Similarly, the antibody molecules of the present invention are preferred to de-polymerize A β -aggregate in vivo and/or in in vitro assays shown in the examples. This capacity of the inventive antibodies/antibody molecules is, inter alia, to be employed in medical settings, in particular in pharmaceutical compositions described herein below.

The invention also provides for a nucleic acid molecule encoding an inventive antibody molecule as defined herein.

Said nucleic acid molecule may be a naturally nucleic acid molecule as well as a recombinant nucleic acid molecule. The nucleic acid molecule of the invention may, therefore, be of natural origin, synthetic or semi-synthetic. It may comprise DNA, RNA as well as PNA and it may be a hybrid thereof.

It is evident to the person skilled in the art that regulatory sequences may be added to the nucleic acid molecule of the invention. For example, promoters, transcriptional enhancers and/or sequences which allow for induced expression of the polynucleotide of the invention may be employed. A suitable inducible system is for

example tetracycline-regulated gene expression as described, e.g., by Gossen and Bujard (Proc. Natl. Acad. Sci. USA 89 (1992), 5547-5551) and Gossen et al. (Trends Biotech. 12 (1994), 58-62), or a dexamethasone-inducible gene expression system as described, e.g. by Crook (1989) EMBO J. 8, 513-519.

Furthermore, it is envisaged for further purposes that nucleic acid molecule may contain, for example, thioester bonds and/or nucleotide analogues. Said modifications may be useful for the stabilization of the nucleic acid molecule against endo- and/or exonucleases in the cell. Said nucleic acid molecules may be transcribed by an appropriate vector containing a chimeric gene which allows for the transcription of said nucleic acid molecule in the cell. In this respect, it is also to be understood that the polynucleotide of the invention can be used for "gene targeting" or "gene therapeutic" approaches. In another embodiment said nucleic acid molecules are labeled. Methods for the detection of nucleic acids are well known in the art, e.g., Southern and Northern blotting, PCR or primer extension. This embodiment may be useful for screening methods for verifying successful introduction of the inventive nucleic acid molecules during gene therapy approaches.

The nucleic acid molecule(s) of the invention may be a recombinantly produced chimeric nucleic acid molecule comprising any of the aforementioned nucleic acid molecules either alone or in combination. Preferably, the nucleic acid molecule of the invention is part of a vector.

The present invention therefore also relates to a vector comprising the nucleic acid molecule of the present invention.

The vector of the present invention may be, e.g., a plasmid, cosmid, virus, bacteriophage or another vector used e.g. conventionally in genetic engineering, and may comprise further genes such as marker genes which allow for the selection of said vector in a suitable host cell and under suitable conditions.

Furthermore, the vector of the present invention may, in addition to the nucleic acid sequences of the invention, comprise expression control elements, allowing proper expression of the coding regions in suitable hosts. Such control elements are known to the artisan and may include a promoter, a splice cassette, translation initiation

codon, translation and insertion site for introducing an insert into the vector. Preferably, the nucleic acid molecule of the invention is operatively linked to said expression control sequences allowing expression in eukaryotic or prokaryotic cells.

Control elements ensuring expression in eukaryotic and prokaryotic cells are well known to those skilled in the art. As mentioned herein above, they usually comprise regulatory sequences ensuring initiation of transcription and optionally poly-A signals ensuring termination of transcription and stabilization of the transcript. Additional regulatory elements may include transcriptional as well as translational enhancers, and/or naturally-associated or heterologous promoter regions. Possible regulatory elements permitting expression in for example mammalian host cells comprise the CMV- HSV thymidine kinase promoter, SV40, RSV-promoter (Rous Sarcoma Virus), human elongation factor 1 α -promoter, the glucocorticoid-inducible MMTV-promoter (Moloney Mouse Tumor Virus), metallothionein- or tetracyclin-inducible promoters, or enhancers, like CMV enhancer or SV40-enhancer. For expression in neural cells, it is envisaged that neurofilament-, PGDF-, NSE-, PrP-, or thy-1-promoters can be employed. Said promoters are known in the art and, inter alia, described in Charron (1995), J. Biol. Chem. 270, 25739-25745. For the expression in prokaryotic cells, a multitude of promoters including, for example, the tac-lac-promoter or the trp promoter, has been described. Besides elements which are responsible for the initiation of transcription such regulatory elements may also comprise transcription termination signals, such as SV40-poly-A site or the tk-poly-A site, downstream of the polynucleotide. In this context, suitable expression vectors are known in the art such as Okayama-Berg cDNA expression vector pcDV1 (Pharmacia), pRc/CMV, pcDNA1, pcDNA3 (In-vitrogene), pSPORT1 (GIBCO BRL), pX (Pagano (1992) Science 255, 1144-1147), yeast two-hybrid vectors, such as pEG202 and dpJG4-5 (Gyuris (1995) Cell 75, 791-803), or prokaryotic expression vectors, such as lambda gt11 or pGEX (Amersham-Pharmacia). Beside the nucleic acid molecules of the present invention, the vector may further comprise nucleic acid sequences encoding for secretion signals. Such sequences are well known to the person skilled in the art. Furthermore, depending on the expression system used leader sequences capable of directing the peptides of the invention to a cellular compartment may be added to the coding sequence of the nucleic acid molecules of the invention and are well

known in the art. The leader sequence(s) is (are) assembled in appropriate phase with translation, initiation and termination sequences, and preferably, a leader sequence capable of directing secretion of translated protein, or a protein thereof, into the periplasmic space or extracellular medium. Optionally, the heterologous sequence can encode a fusionprotein including an C- or N-terminal identification peptide imparting desired characteristics, e.g., stabilization or simplified purification of expressed recombinant product. Once the vector has been incorporated into the appropriate host, the host is maintained under conditions suitable for high level expression of the nucleotide sequences, and, as desired, the collection and purification of the antibody molecules or fragments thereof of the invention may follow. The invention also relates, accordingly, to hosts/host cells which comprise a vector as defined herein. Such hosts may be useful for in processes for obtaining antibodies/antibody molecules of the invention as well as in medical/pharmaceutical settings. Said host cells may also comprise transduced or transfected neuronal cells, like neuronal stem cells, preferably adult neuronal stem cells. Such host cells may be useful in transplantation therapies.

Furthermore, the vector of the present invention may also be an expression, a gene transfer or gene targeting vector. Gene therapy, which is based on introducing therapeutic genes into cells by ex-vivo or in-vivo techniques is one of the most important applications of gene transfer. Transgenic mice expressing a neutralizing antibody directed against nerve growth factor have been generated using the "neuroantibody" technique; Capsoni, Proc. Natl. Acad. Sci. USA 97 (2000), 6826-6831 and Biocca, Embo J. 9 (1990), 101-108. Suitable vectors, methods or gene-delivering systems for in-vitro or in-vivo gene therapy are described in the literature and are known to the person skilled in the art; see, e.g., Giordano, Nature Medicine 2 (1996), 534-539; Schaper, Circ. Res. 79 (1996), 911-919; Anderson, Science 256 (1992), 808-813; Isner, Lancet 348 (1996), 370-374; Muhlhauser, Circ. Res. 77 (1995), 1077-1086; Onodua, Blood 91 (1998), 30-36; Verzeletti, Hum. Gene Ther. 9 (1998), 2243-2251; Verma, Nature 389 (1997), 239-242; Anderson, Nature 392 (Supp. 1998), 25-30; Wang, Gene Therapy 4 (1997), 393-400; Wang, Nature Medicine 2 (1996), 714-716; WO 94/29469; WO 97/00957; US 5,580,859; US 5,589,466; US 4,394,448 or Schaper, Current Opinion in Biotechnology 7 (1996),

635-640, and references cited therein. In particular, said vectors and/or gene delivery systems are also described in gene therapy approaches in neurological tissue/cells (see, inter alia Blömer, J. Virology 71 (1997) 6641-6649) or in the hypothalamus (see, inter alia, Geddes, Front Neuroendocrinol. 20 (1999), 296-316 or Geddes, Nat. Med. 3 (1997), 1402-1404). Further suitable gene therapy constructs for use in neurological cells/tissues are known in the art, for example in Meier (1999), J. Neuropathol. Exp. Neurol. 58, 1099-1110. The nucleic acid molecules and vectors of the invention may be designed for direct introduction or for introduction via liposomes, viral vectors (e.g. adenoviral, retroviral), electroporation, ballistic (e.g. gene gun) or other delivery systems into the cell. Additionally, a baculoviral system can be used as eukaryotic expression system for the nucleic acid molecules of the invention. The introduction and gene therapeutic approach should, preferably, lead to the expression of a functional antibody molecule of the invention, whereby said expressed antibody molecule is particularly useful in the treatment, amelioration and/or prevention of neurological disorders related to abnormal amyloid synthesis, assembly and/or aggregation, like, Alzheimer's disease and the like.

Accordingly, the nucleic acid molecule of the present invention and/or the above described vectors/hosts of the present invention may be particularly useful as pharmaceutical compositions. Said pharmaceutical compositions may be employed in gene therapy approaches. In this context, it is envisaged that the nucleic acid molecules and/or vectors of the present invention may be employed to modulate, alter and/or modify the (cellular) expression and/or concentration of the antibody molecules of the invention or of (a) fragment(s) thereof.

For gene therapy applications, nucleic acids encoding the peptide(s) of the invention or fragments thereof may be cloned into a gene delivering system, such as a virus and the virus used for infection and conferring disease ameliorating or curing effects in the infected cells or organism.

The present invention also relates to a host cell transfected or transformed with the vector of the invention or a non-human host carrying the vector of the present invention, i.e. to a host cell or host which is genetically modified with a nucleic acid

molecule according to the invention or with a vector comprising such a nucleic acid molecule. The term "genetically modified" means that the host cell or host comprises in addition to its natural genome a nucleic acid molecule or vector according to the invention which was introduced into the cell or host or into one of its predecessors/parents. The nucleic acid molecule or vector may be present in the genetically modified host cell or host either as an independent molecule outside the genome, preferably as a molecule which is capable of replication, or it may be stably integrated into the genome of the host cell or host.

The host cell of the present invention may be any prokaryotic or eukaryotic cell. Suitable prokaryotic cells are those generally used for cloning like *E. coli* or *Bacillus subtilis*. Furthermore, eukaryotic cells comprise, for example, fungal or animal cells. Examples for suitable fungal cells are yeast cells, preferably those of the genus *Saccharomyces* and most preferably those of the species *Saccharomyces cerevisiae*. Suitable animal cells are, for instance, insect cells, vertebrate cells, preferably mammalian cells, such as e.g. HEK293, NSO, CHO, MDCK, U2-OSHela, NIH3T3, MOLT-4, Jurkat, PC-12, PC-3, IMR, NT2N, Sk-n-sh, CaSki, C33A. These host cells, e.g. CHO-cells, may provide post-translational modifications to the antibody molecules of the invention, including leader peptide removal, folding and assembly of H (heavy) and L (light) chains, glycosylation of the molecule at correct sides and secretion of the functional molecule. Further suitable cell lines known in the art are obtainable from cell line depositories, like the American Type Culture Collection (ATCC). In accordance with the present invention, it is furthermore envisaged that primary cells/cell cultures may function as host cells. Said cells are in particular derived from insects (like insects of the species *Drosophila* or *Blatta*) or mammals (like human, swine, mouse or rat). Said host cells may also comprise cells from and/or derived from cell lines like neuroblastoma cell lines. The above mentioned primary cells are well known in the art and comprise, inter alia, primary astrocytes, (mixed) spinal cultures or hippocampal cultures.

In a more preferred embodiment the host cell which is transformed with the vector of the invention is a neuronal cell, a neuronal stem cell (e.g. an adult neuronal stem cell), a brain cell or a cell (line) derived therefrom. However, also a CHO-cell

comprising the nucleic acid molecule of the present invention may be particularly useful as host. Such cells may provide for correct secondary modifications on the expressed molecules, i.e. the antibody molecules of the present invention. These modifications comprise, inter alia, glycosylations and phosphorylations.

Hosts may be non-human mammals, most preferably mice, rats, sheep, calves, dogs, monkeys or apes. Said mammals may be indispensable for developing a cure, preferably a cure for neurological and/or neurodegenerative disorders mentioned herein. Furthermore, the hosts of the present invention may be particularly useful in producing the antibody molecules (or fragments thereof) of the invention. It is envisaged that said antibody molecules (or fragments thereof) be isolated from said host. It is, inter alia, envisaged that the nucleic acid molecules and or vectors described herein are incorporated in sequences for transgenic expression. The introduction of the inventive nucleic acid molecules as transgenes into non-human hosts and their subsequent expression may be employed for the production of the inventive antibodies. For example, the expression of such (a) transgene(s) in the milk of the transgenic animal provide for means of obtaining the inventive antibody molecules in quantitative amounts; see inter alia, US 5,741,957, US 5,304,489 or US 5,849,992. Useful transgenes in this respect comprise the nucleic acid molecules of the invention, for example, coding sequences for the light and heavy chains of the antibody molecules described herein, operatively linked to promotor and/or enhancer structures from a mammary gland specific gene, like casein or beta-lactoglobulin.

The invention also provides for a method for the preparation of an antibody molecule of the invention comprising culturing the host cell described herein above under conditions that allow synthesis of said antibody molecule and recovering said antibody molecule from said culture.

The invention also relates to a composition comprising an antibody molecule of the invention or produced by the method described herein above, a nucleic acid molecule encoding the antibody molecule of the invention, a vector comprising said nucleic acid molecule or a host-cell as defined herein above and optionally, further molecules, either alone or in combination, like e.g. molecules which are capable of

interfering with the formation of amyloid plaques or which are capable of depolymerizing already formed amyloid-plaques. The term "composition" as employed herein comprises at least one compound of the invention. Preferably, such a composition is a pharmaceutical or a diagnostic composition.

The composition may be in solid or liquid form and may be, inter alia, in a form of (a) powder(s), (a) tablet(s), (a) solution(s) or (an) aerosol(s). Said composition may comprise on or more antibodies/antibody molecules of the invention or nucleic acid molecules, vector or hosts of the invention. It is also envisaged that said composition comprises at least two, preferably three, more preferably four, most preferably five antibody molecules of the invention or nucleic acid molecule(s) encoding said antibody molecule(s). Said composition may also comprise optimized, inventive antibodies/antibody molecules obtainable by the methods described herein below and in the appended examples.

It is preferred that said pharmaceutical composition, optionally comprises a pharmaceutically acceptable carrier and/or diluent. The herein disclosed pharmaceutical composition may be particularly useful for the treatment of neurological and/or neurodegenerative disorders. Said disorders comprise, but are not limited to Alzheimer's disease, amyotrophic lateral sclerosis (ALS), hereditary cerebral hemorrhage with amyloidosis Dutch type, Down's syndrome, HIV-dementia, Parkinson's disease and neuronal disorders related to aging. The pharmaceutical composition of the invention is, inter alia, envisaged as potent inhibitors of amyloid plaque formation or as a potent stimulator for the de-polymerization of amyloid plaques. Therefore, the present invention provides for pharmaceutical compositions comprising the compounds of the invention to be used for the treatment of diseases/disorders associated with pathological APP proteolysis and/or amyloid plaque formation.

Examples of suitable pharmaceutical carriers, excipients and/or diluents are well known in the art and include phosphate buffered saline solutions, water, emulsions, such as oil/water emulsions, various types of wetting agents, sterile solutions etc. Compositions comprising such carriers can be formulated by well known

conventional methods. These pharmaceutical compositions can be administered to the subject at a suitable dose. Administration of the suitable compositions may be effected by different ways, e.g., by intravenous, intraperitoneal, subcutaneous, intramuscular, topical, intradermal, intranasal or intrabronchial administration. It is particularly preferred that said administration is carried out by injection and/or delivery, e.g., to a site in a brain artery or directly into brain tissue. The compositions of the invention may also be administered directly to the target site, e.g., by biolistic delivery to an external or internal target site, like the brain. The dosage regimen will be determined by the attending physician and clinical factors. As is well known in the medical arts, dosages for any one patient depends upon many factors, including the patient's size, body surface area, age, the particular compound to be administered, sex, time and route of administration, general health, and other drugs being administered concurrently. Proteinaceous pharmaceutically active matter may be present in amounts between 1 ng and 10 mg/kg body weight per dose; however, doses below or above this exemplary range are envisioned, especially considering the aforementioned factors. If the regimen is a continuous infusion, it should also be in the range of 1 µg to 10 mg units per kilogram of body weight per minute.

Progress can be monitored by periodic assessment. The compositions of the invention may be administered locally or systemically. It is of note that peripherally administered antibodies can enter the central nervous system, see, inter alia, Bard (2000), *Nature Med.* 6, 916-919. Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present such as, for example, antimicrobials, anti-oxidants, chelating agents, and inert gases and the like. Furthermore, the pharmaceutical composition of the invention may comprise further agents depending on the intended use of the pharmaceutical composition. Said agents may be drugs acting on the

central nervous system, like, neuroprotective factors, cholinesterase inhibitors, agonists of M1 muscarinic receptor, hormones, antioxidants, inhibitors of inflammation etc. It is particularly preferred that said pharmaceutical composition comprises further agents like, e.g. neurotransmitters and/or substitution molecules for neurotransmitters, vitamin E, or alpha-lipoic acid.

The pharmaceutical compositions, as well as the methods of the invention or the uses of the invention described infra can be used for the treatment of all kinds of diseases hitherto unknown or being related to or dependent on pathological APP aggregation or pathological APP processing. They may be particularly useful for the treatment of Alzheimer's disease and other diseases where extracellular deposits of amyloid- β , appear to play a role. They may be desirably employed in humans, although animal treatment is also encompassed by the methods, uses and compositions described herein.

In a preferred embodiment of the invention, the composition of the present invention as disclosed herein above is a diagnostic composition further comprising, optionally, suitable means for detection. The diagnostic composition comprises at least one of the aforementioned compounds of the invention.

Said diagnostic composition may comprise the compounds of the invention, in particular and preferably the antibody molecules of the present invention, in soluble form/liquid phase but it is also envisaged that said compounds are bound to/attached to and/or linked to a solid support.

Solid supports may be used in combination with the diagnostic composition as defined herein or the compounds of the present invention may be directly bound to said solid supports. Such supports are well known in the art and comprise, inter alia, commercially available column materials, polystyrene beads, latex beads, magnetic beads, colloid metal particles, glass and/or silicon chips and surfaces, nitrocellulose strips, membranes, sheets, duracytes, wells and walls of reaction trays, plastic tubes etc. The compound(s) of the invention, in particular the antibodies of the present invention, may be bound to many different carriers. Examples of well-known carriers include glass, polystyrene, polyvinyl chloride, polypropylene, polyethylene,

polycarbonate, dextran, nylon, amyloses, natural and modified celluloses, polyacrylamides, agaroses, and magnetite. The nature of the carrier can be either soluble or insoluble for the purposes of the invention. Appropriate labels and methods for labeling have been identified above and are furthermore mentioned herein below. Suitable methods for fixing/immobilizing said compound(s) of the invention are well known and include, but are not limited to ionic, hydrophobic, covalent interactions and the like.

It is particularly preferred that the diagnostic composition of the invention is employed for the detection and/or quantification of APP and/or APP-processing products, like amyloid- β or for the detection and/or quantification of pathological and/or (genetically) modified APP-cleavage sides.

As illustrated in the appended examples, the compounds of the present invention, in particular the inventive antibody molecules are particularly useful as diagnostic reagents in the detection of genuine human amyloid plaques in brain sections of Alzheimer's Disease patients by indirect immunofluorescence.

It is preferred that said compounds of the present invention to be employed in a diagnostic composition are detectably labeled. A variety of techniques are available for labeling biomolecules, are well known to the person skilled in the art and are considered to be within the scope of the present invention. Such techniques are, e.g., described in Tijssen, "Practice and theory of enzyme immuno assays", Burden, RH and von Knippenburg (Eds), Volume 15 (1985), "Basic methods in molecular biology"; Davis LG, Diber MD; Battey Elsevier (1990), Mayer et al., (Eds) "Immunochemical methods in cell and molecular biology" Academic Press, London (1987), or in the series "Methods in Enzymology", Academic Press, Inc.

There are many different labels and methods of labeling known to those of ordinary skill in the art. Examples of the types of labels which can be used in the present invention include enzymes, radioisotopes, colloidal metals, fluorescent compounds, chemiluminescent compounds, and bioluminescent compounds.

Commonly used labels comprise, inter alia, fluorochromes (like fluorescein, rhodamine, Texas Red, etc.), enzymes (like horse radish peroxidase, β -galactosidase, alkaline phosphatase), radioactive isotopes (like ^{32}P or ^{125}I), biotin, digoxigenin, colloidal metals, chemi- or bioluminescent compounds (like dioxetanes, luminol or acridiniums). Labeling procedures, like covalent coupling of enzymes or biotinyl groups, iodinations, phosphorylations, biotinylations, etc. are well known in the art.

Detection methods comprise, but are not limited to, autoradiography, fluorescence microscopy, direct and indirect enzymatic reactions, etc. Commonly used detection assays comprise radioisotopic or non-radioisotopic methods. These comprise, inter alia, Westernblotting, overlay-assays, RIA (Radioimmuno Assay) and IRMA (Immune Radioimmunometric Assay), EIA (Enzyme Immuno Assay), ELISA (Enzyme Linked Immuno Sorbent Assay), FIA (Fluorescent Immuno Assay), and CLIA (Chemiluminescent Immune Assay).

Furthermore, the present invention provides for the use of an antibody molecule of invention, or an antibody molecule produced by the method of the invention, of a nucleic acid molecule, vector of or a host of the invention for the preparation of a pharmaceutical or a diagnostic composition for the prevention, treatment and/or diagnosis of a disease associated with amyloidogenesis and/or amyloid-plaque formation. It is further preferred that the compounds described herein, in particular the antibody molecules of the invention, be employed in the prevention and/or treatment of neuropathologies associated with modified or abnormal APP-processing and/or amyloidogenesis. The antibody molecules, e.g. in format of (engineered) immunoglobulins, like antibodies in a IgG framework, in particular in an IgG1-framework, or in the format of chimeric antibodies, bispecific antibodies, single chain Fvs (scFvs) or bispecific scFvs and the like are to be employed in the preparation of the pharmaceutical compositions provided herein. Yet, the antibody molecules are also useful in diagnostic settings as documented in the appended examples, since the antibody molecules of the invention specifically interact with/detect A β 4 and/or amyloid deposits/plaques.

Therefore an inventive use of the compounds of the present invention is the use for the preparation of a pharmaceutical composition for a neurological disorder which calls for amelioration, for example by disintegration of β -amyloid plaques, by amyloid (plaque) clearance or by passive immunization against β -amyloid plaque formation. As illustrated in the appended examples, the inventive antibody molecules are particularly useful in preventing A β aggregation and in de-polymerization of already formed amyloid aggregates. Accordingly, the inventive antibodies are to be employed in the reduction of pathological amyloid deposits/plaques, in the clearance of amyloid plaques/plaque precursors as well as in neuronal protection. It is in particular envisaged that the antibody molecules of the invention be employed in the in vivo prevention of amyloid plaques as well as in in vivo clearance of pre-existing amyloid plaques/deposits. Furthermore, the antibody molecules of the invention may be employed in passive immunization approaches against A β 4. Clearance of A β 4/A β 4 deposits may, inter alia, be achieved by the medical use of antibodies of the present invention which comprise an Fc-part. Said Fc-part of an antibody may be particularly useful in Fc-receptor mediated immune responses, e.g. the attraction of macrophages (phagocytic cells and/or microglia) and/or helper cells. For the mediation of Fc-part-related immunoresponses, the antibody molecule of the invention is preferably in an (human) IgG1- framework. As discussed herein, the preferred subject to be treated with the inventive antibody molecules, the nucleic acid molecules encoding the same or parts thereof, the vectors of the invention or the host cells of this invention is a human subject. Other frameworks, like IgG2a- or IgG2b-frameworks for the inventive antibody molecules are also envisaged. Immunoglobulin frameworks in IgG2a und IgG2b format are particular envisaged in mouse settings, for example in scientific uses of the inventive antibody molecules, e.g. in tests on transgenic mice expressing (human) wildtype or mutated APP, APP-fragments and/or A β 4.

The above recited diseases associated with amyloidogenesis and/or amyloid-plaque formation comprise, but are not limited to dementia, Alzheimer's disease, motor neuropathy, Parkinson's disease, ALS (amyotrophic lateral sclerosis), scrapie, HIV-related dementia as well as Creutzfeld-Jakob disease, hereditary cerebral hemorrhage, with amyloidis Dutch type, Down's syndrome and neuronal disorders

related to aging. The antibody molecules of the invention and the compositions provided herein may also be useful in the amelioration and or prevention of inflammatory processes relating to amyloidogenesis and/or amyloid plaque formation.

Accordingly, the present invention also provides for a method for treating, preventing and/or delaying neurological and/or neurodegenerative disorders comprising the step of administering to a subject suffering from said neurological and/or neurodegenerative disorder and/or to a subject susceptible to said neurological and/or neurodegenerative disorder an effective amount of a antibody molecule of the invention, a nucleic acid molecule of invention and/or a composition as defined herein above.

In yet another embodiment, the present invention provides for a kit comprising at least one antibody molecule, at least one nucleic acid molecule, at least one vector or at least one host cell of the invention. Advantageously, the kit of the present invention further comprises, optionally (a) buffer(s), storage solutions and/or remaining reagents or materials required for the conduct of medical, scientific or diagnostic assays and purposes. Furthermore, parts of the kit of the invention can be packaged individually in vials or bottles or in combination in containers or multicontainer units.

The kit of the present invention may be advantageously used, inter alia, for carrying out the method of the invention and could be employed in a variety of applications referred herein, e.g., as diagnostic kits, as research tools or medical tools. Additionally, the kit of the invention may contain means for detection suitable for scientific, medical and/or diagnostic purposes. The manufacture of the kits follows preferably standard procedures which are known to the person skilled in the art.

The invention also provides for a method for the optimization of an antibody molecule as defined herein above comprising the steps of

(a) constructing a library of diversified Fab antibody fragments derived from an antibody comprising at least one CDR3 of an V_H -region as encoded by a nucleic acid molecule as

shown in SEQ ID NOs: 21, 23 or 25 or at least one CDR3 amino acid sequence of an V_H -region as shown in SEQ ID NOs: 22, 24 or 26;

(b) testing the resulting Fab optimization library by panning against $A\beta/A\beta_4$;

(c) identifying optimized clones; and

(d) expressing of selected, optimized clones.

Optimization of the antibodies/antibody molecules of the invention is also documented in the appended examples and may comprise the selection for, e.g. higher affinity for one or both regions/epitopes of β -A4 as defined herein or selection for improved expression and the like. In one embodiment, said selection for to higher affinity for one or both regions/epitopes of β -A4 comprises the selection for high affinity to (a) an amino acid stretch comprising amino acids 2 to 10 (or (a) part(s) thereof) of β -A4 and/or (b) an amino acid stretch comprising amino acids 12 to 25 (or (a) part(s) thereof) of β -A4 (SEQ ID NO. 27).

The person skilled in the art can readily carry out the inventive method employing the teachings of the present invention. Optimization protocols for antibodies are known in the art. These optimization protocols comprise, inter alia, CDR walking mutagenesis as disclosed and illustrated herein and described in Yang (1995), J. Mol. Biol. 25, 392-403; Schier (1996), J. Mol. Biol. 263, 551-567; Barbas (1996), Trends. Biotech 14, 230-34 or Wu (1998), PNAS 95, 6037-6042; Schier (1996), Human Antibodies Hybridomas 7, 97; Moore (1997), J. Mol. Biol. 272, 336.

"Panning"-techniques are also known in the art, see, e.g. Kay (1993), Gene 128, 59-65. Furthermore, publications like Borrebaeck (1995), "Antibody Engineering", Oxford University, 229-266; McCafferty (1996), "Antibody Engineering", Oxford University Press; Kay (1996), A Laboratory Manual, Academic Press provide for optimization protocols which may be modified in accordance with this invention.

The optimization method may further comprise a step (ca), whereby the optimized clones are further optimized by cassette mutagenesis, as illustrated in the appended examples.

The method for the optimization of an antibody molecule described herein is further illustrated in the appended examples as affinity maturation of parental antibodies

/antibody molecules capable of specifically recognizing two regions of the beta -A4 peptide/ Abeta4/ A β /A β 4/ β A4.

Preferably, said A β /A β 4 (also designated as β A4 in context of this invention) in step (b) of the method described herein above is aggregated A β /A β 4. Said panning may be carried out (as described in the appended examples) with increased stringency of binding. Stringency may be increased, inter alia, by reducing the A β /A β 4 concentration or by elevating the (assay) temperature. The testing of the optimized library by panning is known to the skilled artisan and described in Kay (1993), loc. cit. Preferably, the identification in step (c) is carried out by ranking according to the lowest K_D -values.

Most preferably said identification in step (c) is carried out by koff-ranking. Koff-ranking is known to the skilled artisan and described in Schier (1996), loc. cit.; Schier (1996), J. Mol. Biol. 255, 28-43 or Duenas (1996), Mol. Immunol. 33, 279-286. Furthermore, koff-ranking is illustrated in the appended examples. The off-rate constant may be measured as described in the appended examples.

As mentioned herein above, the identified clones may, for further evaluation, be expressed. The expression may be carried out by known methods, inter alia, illustrated in the appended examples. The expression may, inter alia, lead to expressed Fab-fragments, scFvs, bispecific immunoglobulins, bispecific antibody molecules, Fab- and/or Fv fusion proteins, or full antibodies, like IgGs, in particular IgG1.

Optimized antibodies, in particular optimized Fabs or optimized IgGs, preferably IgG1s, may be tested by methods as illustrated in the appended examples. Such methods comprise, but are not limited to, the testing of binding affinities, the determination of K_D values, pepspot analysis, ELISA-assays, RIA-assays, CLIA-assays, (immuno-) histological studies (for example staining of amyloid plaques), depolymerization assays or antibody-dependent β -A4 phagocytoses.

In a further embodiment of the present invention, a method is provided wherein optimized antibodies are generated by cross-cloning. This method is also illustrated in the appended examples and comprises the step of combining independently

optimized CDR-regions, for example, by combining independently optimized H-CDR2 and L-CDR2 from matured clones with H-CDR3, preferably the same H-CDR3.

In a preferred embodiment, the invention relates to a method for the preparation of a pharmaceutical composition comprising the steps of

- (a) optimization of an antibody according to the method described herein and illustrated in the appended examples; and
- (b) formulating the optimized antibody/antibody molecule with an physiologically acceptable carrier, as described herein above.

Accordingly, the invention also provides for a pharmaceutical composition prepared by the method disclosed herein and comprising further optimized antibody molecules capable of specifically recognizing two regions of the beta-A4 peptide/Abeta4/A β /A4 β /A4, as described herein above.

Exemplified Sequences as recited herein:

SEQ ID NO: 1

AEFRHDSGY

First region of β -A4 peptide, "N-terminal region/epitope"

SEQ ID NO: 2

VHHQKLVFFAEDVG

Second region of β -A4 peptide, "Central/middle region/epitope"

SEQ ID NO: 3

VH-region of MS-Roche#3 (nucleic acid sequence)

CAGGTGCAATTGGTGGAAAGCGGCGGCCTGGTGCACCGGGCGGCAGC
CTGCGTCTGAGCTGCGCGGCCTCCGGATTTACCTTTAGCAGCTATGCGATGAG
CTGGGTGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTGAGCGCGATTAGC
GGTAGCGGCGGCAGCACCTATTATGCGGATAGCGTGAAAGGCCGTTTTACCAT
TTCACGTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGC
GGAAGATACGGCCGTGTATTATTGCGCGCGTCTTACTCATTATGCTCGTTATTA
TCGTTATTTTGATGTTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGC
(SEQ ID NO : 3)

SEQ ID NO: 4

VH-region of MS-Roche#3 (amino acid sequence)

QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGS
GGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARLTHYARYYRYF
DVWGQGTLVTVSS (SEQ ID NO : 4)

SEQ ID NO: 5

VH-region of MS-Roche#7 (nucleic acid sequence)

CAGGTGCAATTGGTGGAAAGCGGCGGCCTGGTGCACCGGGCGGCAGC
CTGCGTCTGAGCTGCGCGGCCTCCGGATTTACCTTTAGCAGCTATGCGATGAG
CTGGGTGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTGAGCGCGATTAGC
GGTAGCGGCGGCAGCACCTATTATGCGGATAGCGTGAAAGGCCGTTTTACCAT
TCACGTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCG
GAAGATACGGCCGTGTATTATTGCGCGCGTGGTAAGGGTAATACTCATAAGCCT
TATGGTTATGTTTCGTTATTTTGATGTTTGGGGCCAAGGCACCCTGGTGACGGTT
AGCTCAGC (SEQ ID NO: 5)

SEQ ID NO: 6

VH-region of MS-Roche#7 (amino acid sequence)

QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGS
GGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGKGNTHKPYGY
VRYFDVWGQGTLVTVSS (SEQ ID NO: 6)

SEQ ID NO: 7

VH-region of MS-Roche#8 (nucleic acid sequence)

CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGC
CTGCGTCTGAGCTGCGCGGCCTCCGATTTACCTTTAGCAGCTATGCGATGAG
CTGGGTGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTGAGCGCGATTAGC
GGTAGCGGCGGCAGCACCTATTATGCGGATAGCGTGAAAGGCCGTTTTACCAT
TTCACGTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGC
GGAAGATACGGCCGTGTATTATTGCGCGCGTCTTCTTTCTCGTGGTTATAATGG
TTATTATCATAAGTTTGATGTTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTC
AGC (SEQ ID NO: 7)

SEQ ID NO: 8

VH-region of MS-Roche#8 (amino acid sequence)

QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGS
GGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARLLSRGYNGYYH
KFDVWGQGTLVTVSS (SEQ ID NO: 8)

SEQ ID NO: 9

VL-region of MS-Roche#3 (nucleic acid sequence)

GATATCGTGCTGACCCAGAGCCCGGCGACCCTGAGCCTGTCTCCGGGCGAAC
GTGCGACCCTGAGCTGCAGAGCGAGCCAGAGCGTGAGCAGCAGCTATCTGGC
GTGGTACCAGCAGAAACCAGGTCAAGCACCGCGTCTATTAATTTATGGCGCGA
GCAGCCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGCAC
GGATTTTACCCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGGTTTATTA
TTGCCAGCAGGTTTATAATCCTCCTGTTACCTTTGGCCAGGGTACGAAAGTTGA
AATTAAACGTACG (SEQ ID NO: 9)

SEQ ID NO: 10

VL-region of MS-Roche #3 (amino acid sequence)

DIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRA
TGVPARFSGSGSGTDFLTLSLEPEDFAVYYCQQVYNPPVTFGQGTKVEIKRT
(SEQ ID NO: 10)

SEQ ID NO: 11

VL-region of MS-Roche#7 (nucleic acid sequence)

GATATCGTGCTGACCCAGAGCCCGGCGACCCTGAGCCTGTCTCCGGGCGAAC
GTGCGACCCTGAGCTGCAGAGCGAGCCAGAGCGTGAGCAGCAGCTATCTGGC

GTGGTACCAGCAGAAACCAGGTCAAGCACCGCGTCTATTAATTTATGGCGCGA
GCAGCCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGCAC
GGATTTTACCCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGACTTATTA
TTGCTTTCAGCTTTATTCTGATCCTTTTACCTTTGGCCAGGGTACGAAAGTTGAA
ATTAAACGTACG (SEQ ID NO. 11)

SEQ ID NO: 12

VL-region of MS-Roche#7 (amino acid sequence)

DIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRA
TGVPARFSGSGSGTDFTLTISSELPEDFATYYCFQLYSDPFTFGQGTKVEIKRT
(SEQ ID NO : 12)

SEQ ID NO: 13

VL-region of MS-Roche#8 (nucleic acid sequence)

GATATCGTGCTGACCCAGAGCCCGGCGACCCTGAGCCTGTCTCCGGGCGAAC
GTGCGACCCTGAGCTGCAGAGCGAGCCAGAGCGTGAGCAGCAGCTATCTGGC
GTGGTACCAGCAGAAACCAGGTCAAGCACCGCGTCTATTAATTTATGGCGCGA
GCAGCCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGCAC
GGATTTTACCCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGACTTATTA
TTGCCAGCAGCTTTCTTCTTTTCCTCCTACCTTTGGCCAGGGTACGAAAGTTGA
AATTAAACGTACG (SEQ ID NO: 13)

SEQ ID NO: 14

VL-region of MS-Roche#8 (amino acid sequence)

DIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRA
TGVPARFSGSGSGTDFTLTISSELPEDFATYYCQQLSSFPPTFGQGTKVEIKRT
(SEQ ID NO : 14)

SEQ ID NO: 15

CDR3 of V_L-region of MSR-3 (nucleic acid sequence)

|CAGCAGGTTTATAATCCTCCTGTT|
(SEQ ID NO : 15)

SEQ ID NO: 16

CDR3 of V_L-region of MSR-3 (amino acid sequence)

QQVYNPPV (SEQ ID NO: 16)

SEQ ID NO: 17

CDR3 of V_L-region of MSR-7 (nucleic acid sequence)

|TTTCAGCTTTATTCTGATCCTTTT|
(SEQ ID NO : 17)

SEQ ID NO: 18

CDR3 of V_L-region of MSR-7 (amino acid sequence)

FQLYSDPF (SEQ ID NO. 18)

SEQ ID NO: 19

CDR3 of V_L-region of MSR-8 (nucleic acid sequence)

CAGCAGCTTTCTTCTTTTCCTCCT
(SEQ ID NO. 19)

SEQ ID NO: 20

CDR3 of V_L-region of MSR-8 (amino acid sequence)

QQLSSFPP (SEQ ID NO: 20)

SEQ ID NO: 21

CDR of V_H-region of MSR-3 (nucleic acid sequence)

CTTACTCATTATGCTCGTTATTATCGTTATTTTGATGTT
(SEQ ID NO: 21)

SEQ ID NO: 22

CDR of V_H-region of MSR-3 (amino acid sequence)

LTHYARYYRYFDV (SEQ ID NO: 22)

SEQ ID NO: 23

CDR of V_H-region of MSR-7 (nucleic acid sequence)

GGTAAGGGTAATACTCATAAGCCTTATGGTTATGTTTCGTTATTTTGATGTT
(SEQ ID NO: 23)

SEQ ID NO: 24

CDR of V_H-region of MSR-7 (amino acid sequence)

GKGNTHKPYGYVRYFDV (SEQ ID NO: 24)

SEQ ID NO: 25

CDR of V_H-region of MSR-8 (nucleic acid sequence)

CTTCTTTCTCGTGGTTATAATGGTTATTATCATAAGTTTGATGTT
(SEQ ID NO. 25)

SEQ ID NO: 26

CDR of V_H-region of MSR-8 (amino acid sequence)

LLSRGYNGYYHKFDV (SEQ ID NO: 26)

SEQ ID NO: 27 Aβ₄ (amino acids 1 to 42)

DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA (SEQ ID NO: 27)

SEQ ID NO: 28 primer

5'-GTGGTGGTTCCGATATC-3' (SEQ ID NO: 28)

SEQ ID NO: 29 primer

5'-AGCGTCACACTCGGTGCGGCTTTCGGCTGGCCAAGAACGGTTA-3' (SEQ ID NO: 29)

SEQ ID NO: 30 primer

5'-CAGGAAACAGCTATGAC-3' (SEQ ID NO: 30)

SEQ ID NO: 31 primer

5'-TACCGTTGCTCTTCACCCC-3' (SEQ ID NO: 31)

SEQ ID NO: 32 V_H of MS-Roche#3.6H5 x 3.6L2; DNA; artificial sequence

CAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTC
TGAGCTGCGCGGCCTCCGGATTACCTTTAGCAGCTATGCGATGAGCTGGGTG
CGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTGAGCGCTATTTCTGAGTCTG
GTAAGACTAAGTATTATGCTGATTCTGTAAAGGGTCGTTTTACCATTTCACGTGA
TAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAAGATAC
GGCCGTGTATTATTGCGCGCGTCTTACTCATTATGCTCGTTATTATCGTTATTTT
GATGTTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA (SEQ ID NO: 32)

SEQ ID NO. 33: prot VH region of MS-Roche#3.6H5 x 3.6L2; protein/1; artificial sequence

QLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWWSAISESGK
TKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARLTHYARYYRYFDV
WGQGTLVTVSS (SEQ ID NO: 33)

SEQ ID NO: 34 VH region of MS-Roche#3.6H8 x 3.6L2; DNA; artificial sequence

CAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTC
TGAGCTGCGCGGCCTCCGGATTTACCTTTAGCAGCTATGCGATGAGCTGGGTG
CGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTGAGCGCTATTTCTGAGTATTC
TAAGTTTAAGTATTATGCTGATTCTGTAAAGGGTCGTTTTACCATTTCACGTGAT
AATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAAGATACG
GCCGTGTATTATTGCGCGCGTCTTACTCATTATGCTCGTTATTATCGTTATTTTG
ATGTTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA (SEQ ID NO: 34)

SEQ ID NO: 35 prot VH region of MS-Roche#3.6H8 x 3.6L2; protein/1; artificial sequence

QLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWWSAISEYSK
FKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARLTHYARYYRYFDV
WGQGTLVTVSS (SEQ ID NO: 35)

SEQ ID NO: 36 VH region of MS-Roche#7.4H2 x 7.2L1; DNA; artificial sequence

CAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTC
TGAGCTGCGCGGCCTCCGGATTTACCTTTAGCAGCTATGCGATGAGCTGGGTG
CGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTGAGCGCTATTAATTATAATGG
TGCTCGTATTTATTATGCTGATTCTGTAAAGGGTCGTTTTACCATTTCACGTGAT
AATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAAGATACG
GCCGTGTATTATTGCGCGCGTGGTAAGGGTAATACTCATAAGCCTTATGGTTAT
GTTCTGTTATTTTGATGTTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
(SEQ ID NO: 36)

SEQ ID NO: 37 prot VH region of MS-Roche#7.4H2 x 7.2L1; protein/1; artificial sequence

QLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWWSAINYNGA
RIYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGKGNTHKPYGYVRY
FDVWGQGT LVT VSS (SEQ ID NO: 37)

SEQ ID NO: 38 VH region of MS-Roche#7.9H2 x 7.12 L2; DNA; artificial sequence
CAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTC
TGAGCTGCGCGGCCTCCGGATTACCTTTAGCAGCTATGCGATGAGCTGGGTG
CGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTGAGCGCTATTAATGCTGATG
GTAATCGTAAGTATTATGCTGATTCTGTTAAGGGTCGTTTTACCATTTCACGTGA
TAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAAGATAC
GGCCGTGTATTATTGCGCGCGTGGTAAGGGTAATACTCATAAGCCTTATGGTTA
TGTTCTTATTTTGATGTTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
(SEQ ID NO: 38)

SEQ ID NO: 39 prot VH region of MS-Roche#7.9H2 x 7.12 L2; protein/1; artificial
sequence
QLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWWSAINADGN
RKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGKGNTHKPYGYVR
YFDVWGQGT LVT VSS (SEQ ID NO: 39)

SEQ ID NO: 40 VH region of MS-Roche#7.9H4 x 7.12L2; DNA; artificial sequence
CAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTC
TGAGCTGCGCGGCCTCCGGATTACCTTTAGCAGCTATGCGATGAGCTGGGTG
CGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTGAGCGCTATTAATGCTGTTGG
TATGAAGAAGTTTTATGCTGATTCTGTTAAGGGTCGTTTTACCATTTCACGTGAT
AATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAAGATACG
GCCGTGTATTATTGCGCGCGTGGTAAGGGTAATACTCATAAGCCTTATGGTTAT
GTTCTTATTTTGATGTTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
(SEQ ID NO: 40)

SEQ ID NO: 41 prot VH region of MS-Roche#7.9H4 x 7.12L2; protein/1; artificial
sequence

QLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAINAVGM
KKFYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGKGNTHKPYGYVR
YFDVWGQGTLVTVSS (SEQ ID NO: 41)

SEQ ID NO: 42 VH region of MS-Roche#7.11H1 x 7.11L1; DNA; artificial sequence
CAATTGGTGGAAAGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTC
TGAGCTGCGCGGCCTCCGGATTTACCTTTAGCAGCTATGCGATGAGCTGGGTG
CGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTGAGCGGTATTAATGCTGCTG
GTTTTCGTACTTATTATGCTGATTCTGTAAAGGGTCGTTTTACCATTTACGTGA
TAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAAGATAC
GGCCGTGTATTATTGCGCGCGTGGTAAGGGTAATACTCATAAGCCTTATGGTTA
TGTTTCGTTATTTTGATGTTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
(SEQ ID NO: 42)

SEQ ID NO. 43 prot VH region of MS-Roche#7.11H1 x 7.11L1; protein/1; artificial
sequence
QLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSGINAAGF
RTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGKGNTHKPYGYVR
YFDVWGQGTLVTVSS (SEQ ID NO: 43)

SEQ ID NO: 44 VH region of MS-Roche#7.11H1 x 7.2L1; DNA; artificial sequence
CAATTGGTGGAAAGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTC
TGAGCTGCGCGGCCTCCGGATTTACCTTTAGCAGCTATGCGATGAGCTGGGTG
CGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTGAGCGGTATTAATGCTGCTG
GTTTTCGTACTTATTATGCTGATTCTGTAAAGGGTCGTTTTACCATTTACGTGA
TAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAAGATAC
GGCCGTGTATTATTGCGCGCGTGGTAAGGGTAATACTCATAAGCCTTATGGTTA
TGTTTCGTTATTTTGATGTTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
(SEQ ID NO: 44)

SEQ ID NO: 45 prot VH region of MS-Roche#7.11H1 x 7.2L1; protein/1; artificial
sequence

QLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSGINAAGF
RTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGKGNTHKPYGYVR
YFDVWGQGTLVTVSS (SEQ ID NO: 45)

SEQ ID NO: 46 VL region of MS-Roche#3.6H5 x 3.6L2; DNA; artificial sequence
GATATCGTGCTGACCCAGAGCCCGGCGACCCTGAGCCTGTCTCCGGGCGAAC
GTGCGACCCTGAGCTGCAGAGCGAGCCAGTTTCTTTCTCGTTATTATCTGGCGT
GGTACCAGCAGAAACCAGGTCAAGCACCGCGTCTATTAATTTATGGCGCGAGC
AGCCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGCACGG
ATTTTACCCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGGTTTATTATTG
CCAGCAGACTTATAATTATCCTCCTACCTTTGGCCAGGGTACGAAAGTTGAAAT
TAAACGTACG (SEQ ID NO: 46)

SEQ ID NO:47 prot VL region of MS-Roche#3.6H5 x 3.6L2; protein/1; artificial
sequence
DIVLTQSPATLSLSPGERATLSCRASQFLSRYYLAWYQQKPGQAPRLLIYGASSRA
TGVPARFSGSGSGTDFTLTISLEPEDFAVYYCQQTYNYPPTFGQGKVEIKRT
(SEQ ID NO: 47)

SEQ ID NO: 48 VL region of MS-Roche#3.6H8 x 3.6L2; DNA; artificial sequence
GATATCGTGCTGACCCAGAGCCCGGCGACCCTGAGCCTGTCTCCGGGCGAAC
GTGCGACCCTGAGCTGCAGAGCGAGCCAGTTTCTTTCTCGTTATTATCTGGCGT
GGTACCAGCAGAAACCAGGTCAAGCACCGCGTCTATTAATTTATGGCGCGAGC
AGCCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGCACGG
ATTTTACCCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGGTTTATTATTG
CCAGCAGACTTATAATTATCCTCCTACCTTTGGCCAGGGTACGAAAGTTGAAAT
TAAACGTACG (SEQ ID NO: 48)

SEQ ID NO: 49 prot VL region of MS-Roche#3.6H8 x 3.6L2; protein/1; artificial
sequence
DIVLTQSPATLSLSPGERATLSCRASQFLSRYYLAWYQQKPGQAPRLLIYGASSRA
TGVPARFSGSGSGTDFTLTISLEPEDFAVYYCQQTYNYPPTFGQGKVEIKRT
(SEQ ID NO: 49)

SEQ ID NO: 50 VL region of MS-Roche#7.4H2 x 7.2L1; DNA; artificial sequence
GATATCGTGCTGACCCAGAGCCCGGCGACCCTGAGCCTGTCTCCGGGCGAAC
GTGCGACCCTGAGCTGCAGAGCGAGCCAGTATGTTGATCGTACTTATCTGGCG
TGGTACCAGCAGAAACCAGGTCAAGCACCGCGTCTATTAATTTATGGCGCGAG
CAGCCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGCACG
GATTTTACCCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGACTTATTATT
GCCAGCAGATTTATTCTTTTCCTCATACCTTTGGCCAGGGTACGAAAGTTGAAAT
TAAACGTACG (SEQ ID NO: 50)

SEQ ID NO: 51 prot VL region of MS-Roche#7.4H2 x 7.2L1; protein/1; artificial
sequence
DIVLTQSPATLSLSPGERATLSCRASQYVDRTYLAWYQQKPGQAPRLLIYGASSRA
TGVPARFSGSGSGTDFTLTISSLEPEDFATYYCQQIYSFPHTFGQGTKVEIKRT
(SEQ ID NO: 51)

SEQ ID NO: 52 VL region of MS-Roche#7.9H2 x 7.12 L2; DNA; artificial sequence
GATATCGTGCTGACCCAGAGCCCGGCGACCCTGAGCCTGTCTCCGGGCGAAC
GTGCGACCCTGAGCTGCAGAGCGAGCCAGCGTTTTTTTTTATAAGTATCTGGCGT
GGTACCAGCAGAAACCAGGTCAAGCACCGCGTCTATTAATTTCTGGTTCTTCTA
ACCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGCACGGA
TTTTACCCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGGTTTATTATTGC
CTTCAGCTTTATAATATTCCTAATACCTTTGGCCAGGGTACGAAAGTTGAAATTA
AACGTACG (SEQ ID NO: 52)

SEQ ID NO: 53 prot VL region of MS-Roche#7.9H2 x 7.12 L2; protein/1; artificial
sequence
DIVLTQSPATLSLSPGERATLSCRASQRFFYKYLAWYQQKPGQAPRLISGSSNRA
TGVPARFSGSGSGTDFTLTISSLEPEDFAVYYCLQLYNIPNTFGQGTKVEIKRT
(SEQ ID NO: 53)

SEQ ID NO: 54 VL region of MS-Roche#7.9H4 x 7.12L2; DNA; artificial sequence

GATATCGTGCTGACCCAGAGCCCGGCGACCCTGAGCCTGTCTCCGGGCGAAC
GTGCGACCCTGAGCTGCAGAGCGAGCCAGCGTTTTTTTTATAAGTATCTGGCGT
GGTACCAGCAGAAACCAGGTCAAGCACCGCGTCTATTAATTTCTGGTTCTTCTA
ACCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGCACGGA
TTTTACCCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGGTTTATTATTGC
CTTCAGCTTTATAATATTCCTAATACCTTTGGCCAGGGTACGAAAGTTGAAATTA
AACGTACG (SEQ ID NO: 54)

SEQ ID NO: 55 prot VL region of MS-Roche#7.9H4 x 7.12L2; protein/1; artificial sequence

DIVLTQSPATLSLSPGERATLSCRASQRFFYKYLAWYQQKPGQAPRLLISGSSNRA
TGVPARFSGSGSGTDFTLTISSELPEDFAVYYCLQLYNIPNTFGQGTKVEIKRT
(SEQ ID NO: 55)

SEQ ID NO: 56 VL region of MS-Roche#7.11H1 x 7.11L1; DNA; artificial sequence

GATATCGTGCTGACCCAGAGCCCGGCGACCCTGAGCCTGTCTCCGGGCGAAC
GTGCGACCCTGAGCTGCAGAGCGAGCCAGCGTATTCTTCGTATTTATCTGGCG
TGGTACCAGCAGAAACCAGGTCAAGCACCGCGTCTATTAATTTATGGCGCGAG
CAGCCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGCACG
GATTTTACCCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGACTTATTATT
GCCAGCAGGTTTATTCTCCTCCTCATACCTTTGGCCAGGGTACGAAAGTTGAAA
TTAAACGTACG (SEQ ID NO: 56)

SEQ ID NO: 57 prot VL region of MS-Roche#7.11H1 x 7.11L1; protein/1; artificial sequence

DIVLTQSPATLSLSPGERATLSCRASQRILRIYLAWYQQKPGQAPRLLIYGASSRAT
GVPARFSGSGSGTDFTLTISSELPEDFATYYCQVYSPPHFTFGQGTKVEIKRT
(SEQ ID NO: 57)

SEQ ID NO: 58 VL region of MS-Roche#7.11H1 x 7.2L1; DNA; artificial sequence

GATATCGTGCTGACCCAGAGCCCGGCGACCCTGAGCCTGTCTCCGGGCGAAC
GTGCGACCCTGAGCTGCAGAGCGAGCCAGTATGTTGATCGTACTTATCTGGCG
TGGTACCAGCAGAAACCAGGTCAAGCACCGCGTCTATTAATTTATGGCGCGAG

CAGCCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGGCACG
GATTTTACCCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGACTTATTATT
GCCAGCAGATTTATTCTTTTCCTCATACCTTTGGCCAGGGTACGAAAGTTGAAAT
TAAACGTACG (SEQ ID NO: 58)

SEQ ID NO: 59 prot VL region of MS-Roche#7.11H1 x 7.2L1; protein/1; artificial
sequence

DIVLTQSPATLSLSPGERATLSCRASQYVDRTYLAWYQQKPGQAPRLLIYGASSRA
TGVPARFSGSGSGTDFTLTISSELPEDFATYYCQQIYSFPHTFGQGTKVEIKRT
(SEQ ID NO: 59)

SEQ ID NO: 60 HCDR3 region of MS-Roche#3.6H5 x 3.6L2; DNA; artificial
sequence

CTTACTCATTATGCTCGTTATTATCGTTATTTTGATGTT (SEQ ID NO: 60)

SEQ ID NO: 61 prot HCDR3 region of MS-Roche#3.6H5 x 3.6L2; protein/1; artificial
sequence

LTHYARYYRYFDV (SEQ ID NO: 61)

SEQ ID NO: 62 HCDR3 region of MS-Roche#3.6H8 x 3.6L2; DNA; artificial
sequence

CTTACTCATTATGCTCGTTATTATCGTTATTTTGATGTT (SEQ ID NO: 62)

SEQ ID NO: 63 prot HCDR3 region of MS-Roche#3.6H8 x 3.6L2; protein/1; artificial
sequence

LTHYARYYRYFDV (SEQ ID NO: 63)

SEQ ID NO: 64 HCDR3 region of MS-Roche#7.4H2 x 7.2L1; DNA; artificial
sequence

GGTAAGGGTAATACTCATAAGCCTTATGGTTATGTTTCGTTATTTTGATGTT (SEQ
ID NO: 64)

SEQ ID NO: 65 prot HCDR3 region of MS-Roche#7.4H2 x 7.2L1; protein/1; artificial sequence

GKGNTHKPYGYVRYFDV (SEQ ID NO: 65)

SEQ ID NO: 66 HCDR3 region of MS-Roche#7.9H2 x 7.12 L2; DNA; artificial sequence

GGTAAGGGTAATACTCATAAGCCTTATGGTTATGTTTCGTTATTTTGATGTT (SEQ ID NO: 66)

SEQ ID NO: 67 prot HCDR3 region of#MS-Roche 7.9H2 x 7.12 L2; protein/1; artificial sequence

GKGNTHKPYGYVRYFDV (SEQ ID NO: 67)

SEQ ID NO: 68 HCDR3 region of MS-Roche#7.9H4 x 7.12L2; DNA; artificial sequence

GGTAAGGGTAATACTCATAAGCCTTATGGTTATGTTTCGTTATTTTGATGTT (SEQ ID NO: 68)

SEQ ID NO: 69 prot HCDR3 region of MS-Roche#7.9H4 x 7.12L2; protein/1; artificial sequence

GKGNTHKPYGYVRYFDV (SEQ ID NO: 69)

SEQ ID NO: 70 HCDR3 region of MS-Roche#7.11H1 x 7.11L1; DNA; artificial sequence

GGTAAGGGTAATACTCATAAGCCTTATGGTTATGTTTCGTTATTTTGATGTT (SEQ ID NO: 70)

SEQ ID NO: 71 prot HCDR3 region of MS-Roche#7.11H1 x 7.11L1; protein/1; artificial sequence

GKGNTHKPYGYVRYFDV (SEQ ID NO: 71)

SEQ ID NO: 72 HCDR3 region of MS-Roche#7.11H1 x 7.2L1; DNA; artificial sequence

GGTAAGGGTAATACTCATAAGCCTTATGGTTATGTTTCGTTATTTTGATGTT (SEQ ID NO: 72)

SEQ ID NO: 73 prot HCDR3 region of MS-Roche#7.11H1 x 7.2L1; protein/1; artificial sequence
GKGNTHKPYGYVRYFDV (SEQ ID NO: 73)

SEQ ID NO: 74 LCDR3 region of MS-Roche#3.6H5 x 3.6L2; DNA; artificial sequence
CAGCAGACTTATAATTATCCTCCT (SEQ ID NO: 74)

SEQ ID NO: 75 prot LCDR3 region of MS-Roche#3.6H5 x 3.6L2; protein/1; artificial sequence
QQTYNYP (SEQ ID NO: 75)

SEQ ID NO: 76 LCDR3 region of MS-Roche#3.6H8 x 3.6L2; DNA; artificial sequence
CAGCAGACTTATAATTATCCTCCT (SEQ ID NO: 76)

SEQ ID NO: 77 prot LCDR3 region of MS-Roche#3.6H8 x 3.6L2; protein/1; artificial sequence
QQTYNYP (SEQ ID NO: 77)

SEQ ID NO: 78 LCDR3 region of MS-Roche#7.4H2 x 7.2L1; DNA; artificial sequence
CAGCAGATTTATTCTTTTCCTCAT (SEQ ID NO: 78)

SEQ ID NO: 79 prot LCDR3 region of MS-Roche#7.4H2 x 7.2L1; protein/1; artificial sequence
QQIYSFP (SEQ ID NO: 79)

SEQ ID NO: 80 LCDR3 region of MS-Roche#7.9H2 x 7.12 L2; DNA; artificial sequence

CTTCAGCTTTATAATATTCCTAAT (SEQ ID NO: 80)

SEQ ID NO: 81 prot LCDR3 region of MS-Roche#7.9H2 x 7.12 L2; protein/1; artificial sequence

LQLYNIPN (SEQ ID NO: 81)

SEQ ID NO: 82 LCDR3 region of MS-Roche#7.9H4 x 7.12L2; DNA; artificial sequence

CTTCAGCTTTATAATATTCCTAAT (SEQ ID NO: 82)

SEQ ID NO: 83 prot LCDR3 region of MS-Roche#7.9H4 x 7.12L2; protein/1; artificial sequence

LQLYNIPN (SEQ ID NO: 83)

SEQ ID NO: 84 LCDR3 region of MS-Roche#7.11H1 x 7.11L1; DNA; artificial sequence

CAGCAGGTTTATTCTCCTCCTCAT (SEQ ID NO: 84)

SEQ ID NO: 85 prot LCDR3 region of MS-Roche#7.11H1 x 7.11L1; protein/1; artificial sequence

QQVYSPPH (SEQ ID NO: 85)

SEQ ID NO: 86 LCDR3 region of MS-Roche#7.11H1 x 7.2L1; DNA; artificial sequence

CAGCAGATTTATTCTTTTCCTCAT (SEQ ID NO: 86)

SEQ ID NO: 87 prot LCDR3 region of MS-Roche#7.11H1 x 7.2L1; protein/1; artificial sequence

QQIYSFPH (SEQ ID NO: 87)

SEQ ID NO: 88 VH region of MS-Roche#7.9H7; DNA; artificial sequence

Cagggtgcaattgggtggaaagcggcgggcggcctgggtgcaaccggggcggcagcctgcgtctgagctgcgcggcctc
cggatttaccttagcagctatgcgatgagctgggtgcgccaagcccctgggaagggtctcgagtgggtgagcgctat

taatgcttctgggtactcggtacttattatgctgattctgttaagggcgctttaccatttcacgtgataattcgaaaaacaccctg
tatctgcaaatgaacagcctgctgcggaagatacggccgtgtattattgcgcgctggtaagggtaataactcataag
ccttatgggtatgttcgttattttgatgtttggggccaaggcaccctggtagcggttagctca (SEQ ID NO: 88)

SEQ ID NO: 89 prot VH region of MS-Roche#7.9H7; protein/1; artificial sequence
QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAINAS
GTRTYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGKGNTHKPYGY
VRYFDVWGQGLTVTVSS (SEQ ID NO: 89)

SEQ ID NO: 90 VL region of MS-Roche#7.9H7; DNA; artificial sequence
Gatatcgtgctgaccagagcccggcgaccctgagcctgtctccgggcgaacgtgcgaccctgagctgcagagcg
agccagagcgtgagcagcagctatctggcgtggtagcagcagaaccagggtcaagcaccgcgtctattaatttatg
gcgcgagcagccgtgcaactgggggtccggcgcgcttttagcggctctggatccggcacggattttaccctgaccatta
gcagcctggaacctgaagactttgcgacttattattgccttcagattataatatgcctattacctttggccaggggtacgaa
agttgaaattaaacgtacg (SEQ ID NO: 90)

SEQ ID NO: 91 prot VL region of MS-Roche#7.9H7; protein/1; artificial sequence
DIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRA
TGVPARFSGSGSGTDFTLTISSELPEDFATYYCLQIYNMPITFGQGTKVEIKRT
(SEQ ID NO: 91)

SEQ ID NO: 92 HCDR3 region of MS-Roche#7.9H7; DNA; artificial sequence
Ggtaagggtaataactcataagcccttatgggtatgttcgttattttgatgtt (SEQ ID NO: 92)

SEQ ID NO: 93 prot HCDR3 region of MS-Roche#7.9H7; protein/1; artificial
sequence
GKGNTHKPYGYVRYFDV (SEQ ID NO: 93)

SEQ ID NO: 94 LCDR3 region of MS-Roche#7.9H7; DNA; artificial sequence
Cttcagatttataatatgcctatt (SEQ ID NO: 94)

SEQ ID NO: 95 prot LCDR3 region of MS-Roche#7.9H7; protein/1; artificial
sequence

LQIYNMPI (SEQ ID NO: 95)

Further illustrative sequences are depicted in the appended sequence listing and are also shown in the appended tables, in particular tables 1, 8 and 10.

The Figures show:

Figure 1 Sequence summary of HuCAL[®]-Fab1 Library

The numbering is according to VBASE except the gap in VL λ position 9. In VBASE the gap is set at position 10 (*Chothia et al., 1992*). In the sequence summary all CDR3 residues which were kept constant are indicated. Corresponding sequences employed for the HuCAL-Fab1 library can be found in the appended sequence listing.

A: amino acid sequence

B: DNA sequence

Figure 2 Fab display vector pMORPH[®]18_Fab

Vector map and DNA sequence including restriction sites

Figure 3 Fab expression vector pMORPH[®]x9_Fab

Vector map and DNA sequence including restriction sites

Figure 4 Sequences of the parental Fab fragments MS-Roche-3, MS-Roche-7 and MS-Roche 8

A: amino acid sequence

B: DNA sequence

Figure 5: Indirect immunofluorescence of amyloid-plaques from a cryostat section of human temporal cortex. The plaques were labeled with MS-R # 3.2 Fab (upper panels) and MS-R # 7.4 Fab (lower panels) at 20 μ g/ml (left panels) and 5 μ g/ml (right panels) under stringent blocking conditions. Bound MS-R Fab was revealed by goat anti-human-Cy3.

Figure 6: Indirect immunofluorescence of amyloid-plaques from a cryostat section of human temporal cortex. The plaques were labeled with MS-R # 3.3 IgG1 (upper panels) and MS-R # 7.12 IgG1 (lower panels) at 0.05 µg/ml (left panels) and 0.01 µg/ml (right panels) under stringent blocking conditions. Bound MS-R IgG1 antibody was revealed by goat anti-human (H+L)-Cy3.

Figure 7: Indirect immunofluorescence of amyloid-plaques from a cryostat section of human temporal cortex using antibodies after final affinity maturation. The plaques were labeled with MS-R # 7.9.H7 IgG1 (MAB 31, top panel), MS-R # 7.11.H1x7.2.L1 IgG1 (MAB 11, middle panel) and MS-R # 3.4.H7, bottom panel). Antibodies were used at 0.05 µg/ml (left panels) and 0.01 µg/ml (right panels) under stringent blocking conditions. Bound MS-R IgG1 antibody was revealed by goat anti-human (H+L)-Cy3.

Scale: 8,5 mm = 150 µm.

Figure 8: Polymerization Assay. Anti-A β antibodies prevent incorporation of biotinylated A β into preformed A β aggregates.

Figure 9: De-polymerization Assay. Anti-A β antibodies induce release of biotinylated A β from aggregated A β .

Figure 10: *In vivo* decoration of amyloid plaques in an APP/PS2 double transgenic mouse after intravenous injection of 1mg MS-Roche IgG #7.9.H2 x 7.12.L2. After three days the mouse was perfused with phosphate-buffered saline and sacrificed. The presence of human IgG bound to amyloid plaques was revealed by confocal microscopy after labelling cryostat sections from the frontal cortex with a goat anti-human IgG-Cy3 conjugate (panel B). The same section was counterstained with an anti-A β mouse monoclonal antibody (BAP-2-Alexa488 conjugate, panel A) to visualize the position of amyloid plaques. Individual red

(panel B) and green (panel A) channels, merged image (panel D) and colocalized (panel C) signals are shown.

Scale: 1 cm = 50 μ m

Figure 11: *In vivo* decoration of amyloid plaques in an APP/PS2 double transgenic mouse after intravenous injection of 1mg MS-Roche IgG #7.9.H4 x 7.12.L2. Experimental conditions and staining procedure were identical to those described in the legend of figure 10.

Scale: 1.6 cm = 50 μ m

Figure 12: *In vivo* decoration of amyloid plaques in an APP/PS2 double transgenic mouse after intravenous injection of 1mg MS-Roche IgG #7.11.H1 x 7.2.L1 (MAB 11). Experimental conditions and staining procedure were identical to those described in the legend of figure 10.

Scale: 1.4 cm = 70 μ m

Figure 13: *In vivo* decoration of amyloid plaques in an APP/PS2 double transgenic mouse after intravenous injection of 2 mg MS-Roche IgG #7.9.H7 (MAB 31) at day 0, 3, and 6. After nine days the mouse was perfused with phosphate-buffered saline and sacrificed. The presence of human IgG bound to amyloid plaques was revealed by confocal microscopy after labelling cryostat sections from the frontal cortex with a goat anti-human IgG-Cy3 conjugate (panel B). The same section was counterstained with an anti-A β mouse monoclonal antibody (BAP-2-Alexa488 conjugate, panel A) to visualize the position of amyloid plaques. Individual red (panel B) and green (panel A) channels, merged image (panel D) and colocalized (panel C) signals and are shown.

Scale: 1.6 cm = 80 μ m (panels A, B, C); 1.0 cm = 50 μ m (panel D)

Figure 14: *In vivo* decoration of amyloid plaques in an APP/PS2 double transgenic mouse after intravenous injection of 2 mg MS-Roche IgG #7.11.H1 x 7.2.L1 (MAB 11) at day 0, 3 and 6. Experimental conditions and

staining procedure were identical to those described in the legend of figure 13.

Scale: 1.6 cm = 80 μ m

Figure 15: Binding analysis of anti-A β antibodies to cell surface APP. Antibody binding to human APP-transfected HEK293 cells and non-transfected control cells was analyzed by flow cytometry.

The examples illustrate the invention.

Example 1: Construction and Screening of a Human Combinatorial Antibody Library (HuCAL[®]-Fab 1)

Cloning of HuCAL[®]-Fab 1

HuCAL[®]-Fab 1 is a fully synthetic, modular human antibody library in the Fab antibody fragment format. HuCAL[®]-Fab 1 was assembled starting from an antibody library in the single-chain format (HuCAL[®]-scFv; *Knappik, (2000), J. Mol. Biol. 296, 57-86*).

VL positions 1 and 2. The original HuCAL[®] master genes were constructed with their authentic N-termini: VL λ 1: QS (CAGAGC), VL λ 2: QS (CAGAGC), and VL λ 3: SY (AGCTAT). Sequences containing these amino acids are shown in WO 97/08320. During HuCAL[®] library construction, the first two amino acids were changed to DI to facilitate library cloning (*EcoRI* site). All HuCAL[®] libraries contain VL λ genes with the *EcoRV* site GATATC (DI) at the 5'-end. All HuCAL[®] kappa genes (master genes and all genes in the library) contain DI at the 5'-end (figure 1 A and B).

VH position 1. The original HuCAL[®] master genes were constructed with their authentic N-termini: VH1A, VH1B, VH2, VH4, and VH6 with Q (=CAG) as the first amino acid and VH3 and VH5 with E (=GAA) as the first amino acid. Sequences containing these amino acids are shown in WO 97/08320. During cloning of the HuCAL[®]-Fab1 library, amino acid at position 1 of VH was changed to Q (CAG) in all VH genes (figure 1 A and B).

Design of the CDR libraries

V κ 1/V κ 3 position 85. Because of the cassette mutagenesis procedure used to introduce the CDR3 library (Knappik, (2000), *loc. cit.*), position 85 of V κ 1 and V κ 3 can be either T or V. Thus, during HuCAL[®]-scFv1 library construction, position 85 of V κ 1 and V κ 3 was varied as follows: V κ 1 original, 85T (codon ACC); V κ 1 library, 85T or 85V (TRIM codons ACT or GTT); V κ 3 original, 85V (codon GTG); V κ 3 library, 85T or 85V (TRIM codons ACT or GTT); the same applies to HuCAL[®]-Fab1.

CDR3 design. All CDR3 residues, which were kept constant, are indicated in figure 1 A and B.

CDR3 length. The designed CDR3 length distribution is as follows. Residues, which were varied are shown in brackets (x) in figure 1. V kappa CDR3, 8 amino acid residues (position 89 to 96) (occasionally 7-10 residues), with Q89, S90, and D92 fixed; and VH CDR3, 5 to 28 amino acid residues (position 95 to 102) (occasionally 4-28), with D101 fixed.

HuCAL[®]-Fab 1 was cloned into a phagemid expression vector pMORPH[®]18_Fab1 (figure 2). This vector comprises the Fd fragment with a phoA signal sequence fused at the C-terminus to a truncated gene III protein of filamentous phage, and further comprises the light chain VL-CL with an ompA signal sequence. Both chains are under the control of the lac operon. The constant domains C λ , C κ and CH1 are synthetic genes fully compatible with the modular system of HuCAL[®] (Knappik, (2000), *loc. cit.*).

The whole VH-chain (*MunI/StyI*-fragment) was replaced by a 1205 bp dummy fragment containing the β -lactamase transcription unit (*bla*), thereby facilitating subsequent steps for vector fragment preparation and allowing for selection of complete VH removal.

After VH-replacement, VL λ was removed by *EcoRI/DraIII* and VL κ by *EcoRI/BsiWI* and replaced with bacterial alkaline phosphatase (*bap*) gene fragment (1420 bp).

As the variability of the light chains is lower than that of the heavy chains, cloning was started with the light chain libraries. The VL λ and VL κ light chain libraries diversified in L-CDR3, which were generated for the HuCAL[®]-scFv library (Knappik, (2000), *loc. cit.*) were also used for cloning of HuCAL[®]-Fab1. In case of λ they consisted of the λ 1-, λ 2- and λ 3-HuCAL[®]-framework and had a total variability of 5.7

$\times 10^6$. VL $_{\lambda}$ fragments were amplified by 15 PCR cycles (Pwo-polymerase) with primers 5'-GTGGTGGTTCCGATATC-3' (SEQ ID NO: 28) and 5'-AGCGTCACACTCGGTGCGGCTTTCGGCTGGCCAAGAACGGTTA-3' (SEQ ID NO: 29). PCR-products were digested with *EcoRV/DraIII* and gel-purified. In case of the VL $_{\lambda}$ -library, the *bap*-dummy was removed by *EcoRV/DraIII* from the library vector. 2 μ g of gelpurified vector were ligated with a 3-fold molar excess of VL $_{\lambda}$ -chains for 16 h at 16°C, and the ligation mixtures were electroporated in 800 μ l *E. coli* TOP10F cells (Invitrogen), yielding altogether 4.1×10^8 independent colonies. The transformants were amplified about 2000-fold in 2 x YT/1% glucose/34 μ g/ml chloramphenicol/100 μ g/ml ampicillin, harvested and stored in 20% (w/v) glycerol at -80°C.

The κ libraries comprise the $\kappa 1$ -, $\kappa 2$ -, $\kappa 3$ - and $\kappa 4$ -HuCAL[®] master genes with a total variability of 5.7×10^6 . VL $_{\kappa}$ -chains were obtained by restriction digest with *EcoRV/BsWI* and gel-purified. In case of the VL $_{\kappa}$ -library, the *bap*-dummy was removed by *EcoRV/BsWI* from the library vector. 2 μ g of gel-purified vector were mixed with a 5-fold molar excess of VL $_{\kappa}$ -chains. Ligation and transformation into *E. coli* TOP10F cells (Invitrogen) was performed as described for VL $_{\lambda}$ -chains, yielding altogether 1.6×10^8 independent colonies.

DNA of the two light chain libraries was prepared and the *bla*-dummy was removed by *MunII/StyI*, thereby generating the two vectors for insertion of the VH sub-libraries. The VH libraries of HuCAL[®]-scFv were used for the generation of HuCAL[®]-Fab1. The VH libraries of HuCAL[®]-scFv consist of the master genes VH1A/B-6 diversified with two VH-CDR3 trinucleotide library cassettes differing in CDR3 length separately, and each VH-library combined with the VL $_{\kappa}$ - and with the VL $_{\lambda}$ -library. For the generation of the HuCAL[®]-Fab1 DNA from these VH-libraries was prepared preserving the original variability. The DNA was digested with *MunII/StyI* and gel-purified. A 5-fold molar excess of the VH-chains was ligated with 3 μ g of the VL $_{\lambda}$ -library vector and with 3 μ g of the VL $_{\kappa}$ -library vector for 4 h at 22°C. The ligation mixtures were electroporated for each vector in 1200 μ l *E. coli* TOP10F cells (Invitrogen), yielding altogether 2.1×10^{10} independent colonies. The transformants were amplified about 4000-fold in 2 x YT/1% glucose/34 μ g/ml chloramphenicol/10 μ g/ml tetracycline, harvested and stored in 20% (w/v) glycerol at -80°C.

As quality control the light chain and heavy chain of single clones was sequenced with 5'-CAGGAAACAGCTATGAC-3' (SEQ ID NO: 30) and 5'-TACCGTTGCTCTTCACCCC-3' (SEQ ID NO: 31), respectively.

Phagemid rescue, phage amplification and purification

HuCAL[®]-Fab 1 was amplified in 2 x TY medium containing 34 µg/ml chloramphenicol, 10 µg/ml tetracycline and 1 % glucose (2 x TY-CG). After helper phage infection (VCSM13) at 37°C at an OD₆₀₀ of about 0.5, centrifugation and resuspension in 2 x TY / 34 µg/ml chloramphenicol / 50 µg/ml kanamycin cells were grown overnight at 30°C. Phage were PEG-precipitated from the supernatant (Ausubel, (1998), Current protocols in molecular biology. John Wiley & Sons, Inc., New York, USA), resuspended in PBS/20% glycerol and stored at -80°C. Phage amplification between two panning rounds was conducted as follows: mid-log phase TG1-cells were infected with eluted phage and plated onto LB-agar supplemented with 1% of glucose and 34 µg/ml of chloramphenicol. After overnight incubation at 30°C colonies were scraped off, adjusted to an OD₆₀₀ of 0.5 and helper phage added as described above.

Example 2: Solid phase panning

Wells of MaxiSorp[™] microtiterplates F96 (Nunc) were coated with 100 µl 2.5 µM human Aβ (1-40) peptide (Bachem) dissolved in TBS containing NaN₃ (0.05% v/v) and the sealed plate was incubated for 3 days at 37 °C where the peptide is prone to aggregate on the plate. After blocking with 5% non-fat dried milk in TBS, 1–5 x 10¹² HuCAL[®]-Fab phage purified as above were added for 1h at 20°C. After several washing steps, bound phages were eluted by pH-elution with 500 mM NaCl, 100 mM glycine pH 2.2 and subsequent neutralisation with 1M TRIS-Cl pH 7. Three rounds of panning were performed with phage amplification conducted between each round as described above, the washing stringency was increased from round to round.

Example 3: Subcloning of selected Fab fragments for expression

The Fab-encoding inserts of the selected HuCAL[®]-Fab fragments were subcloned into the expression vector pMORPH[®]x7_FS to facilitate rapid expression of soluble Fab. The DNA preparation of the selected HuCAL[®]-Fab clones was digested with *XbaI/EcoRI*, thus cutting out the Fab encoding insert (ompA-VL and phoA-Fd). Subcloning of the purified inserts into the *XbaI/EcoRI* cut vector pMORPH[®]x7, previously carrying a scFv insert, leads to a Fab expression vector designated pMORPH[®]x9_Fab1 (figure 3). Fabs expressed in this vector carry two C-terminal tags (FLAG and Strep) for detection and purification.

Example 4: Identification of A β -binding Fab fragments by ELISA

Wells of Maxisorp[™] microtiterplates F384 (Nunc) were coated with 20 μ l 2.5 μ M human A β (1-40) peptide (Bachem) dissolved in TBS containing NaN₃ (0.05% v/v) and the sealed plate was incubated for 3 days at 37 °C, where the peptide is prone to aggregate on the plate. Expression of individual Fab was induced with 1 mM IPTG for 16 h at 22°C. Soluble Fab was extracted from *E. coli* by BEL lysis (boric acid, NaCl, EDTA and lysozyme containing buffer pH 8) and used in an ELISA. The Fab fragment was detected with an alkaline phosphatase-conjugated goat anti-Fab antibody (Dianova/Jackson Immuno Research). After excitation at 340 nm the emission at 535 nm was read out after addition of AttoPhos fluorescence substrate (Roche Diagnostics).

Example 5: Optimization of antibody fragments

In order to optimize the binding affinity of the selected A β binding antibody fragments, some of the Fab fragments, MS-Roche-3 (MSR-3), MS-Roche-7 (MSR-7) and MS-Roche-8 (MSR-8) (figure 4), were used to construct a library of Fab antibody fragments by replacing the parental VL κ 3 chain by the pool of all kappa chains κ 1-3 diversified in CDR3 from the HuCAL[®] library (*Knappik et al., 2000*).

The Fab fragments MS-Roche-3, 7 and 8 were cloned via *XbaI/EcoRI* from pMORPH[®]x9_FS into pMORPH[®]18, a phagemid-based vector for phage display of

Fab fragments, to generate pMORPH[®]18_Fab1 (figure 2). A kappa chain pool was cloned into pMORPH[®]18_Fab1 via *XbaI/SphI* restriction sites.

The resulting Fab optimization library was screened by panning against aggregated human A β (1-40) peptide coated to a solid support as described in example 2.

Optimized clones were identified by koff-ranking in a Biacore assay as described in Example 8. The optimized clones MS-Roche-3.2, 3.3, 3.4, 3.6, 7.2, 7.3, 7.4, 7.9, 7.11, 7.12, 8.1, 8.2, were further characterized and showed improved affinity and biological activity compared to the starting fragment MS-Roche-3, MS-Roche-7 and MS-Roche-8 (figure 4). The CDRs listed refer to the HuCAL[®] consensus-based antibody gene VH3kappa3. The Fab fragment MS-Roche-7.12 was obtained by cloning the HCDR3 of parental clone MS-R 7 into a HuCAL[®]-Fab library, carrying diversity in all 6 CDR regions using a design procedure identical with that for CDR3 cassettes described in Knappik *et al.*, 2000. The library cassettes were designed strongly biased for the known natural distribution of amino acids and following the concept of canonical CDR conformations established by Allazikani (Allazikani *et al.*, 1997). However in contrast to the HuCAL[®] master genes, the clone MS-Roche 7.12 contains amino acid S at position 49 of the VL chain (see appended table 1).

The optimized Fabs after the first affinity maturation round showed improved characteristics over the starting MS-Roche-3, MS-Roche-7 and MS-Roche-8 clones (Figure 4). The binding affinities of the matured Fabs to A β 1-40 and A β 1-42 were significantly increased yielding K_D values in the range of 22 – 240 nM in comparison to 850 – 1714 nM of the parental clones (Table 3). Immunohistochemistry analysis of amyloid plaques in human AD brain sections also showed a significantly increased staining profile of the matured clones, i. e. better signal to background ratios were obtained and positive plaque staining was detected at relatively low concentrations of the matured Fabs (Figure 5).

For further optimization, the VH CDR2 regions and the VL CDR1 regions of a set of antibody fragments derived from L-CDR3 optimized MS-Roche-3, -7 and -8 (table 1; figure 4) were optimized by cassette mutagenesis using trinucleotide-directed mutagenesis (Virnekäs *et al.*, 1994). Therefore, a trinucleotide-based HCDR2

cassette and a trinucleotide-based LCDR1 cassette were constructed using a design procedure identical with that for CDR3 cassettes described in Knappik *et al.*, 2000. The library cassettes were designed strongly biased for the known natural distribution of amino acids and following the concept of canonical CDR conformations established by Allazikani (Allazikani *et al.*, 1997). The protocol used for the optimization of the initial selected antibody fragments would mimic the process of affinity maturation by somatic hypermutation observed during the natural immune response.

The resulting libraries were screened separately as described above leading to optimized clones either in the H-CDR2 or in the L-CDR1 region. All clones were identified as above by an improved koff towards A β 1-40-fibers after a koff-ranking in the Biacore and showed improved affinity either to A β 1-40 or A β -42 or both when compared to the corresponding parent clone (Table 3). Table 1 contains the sequence characteristics of the parental as well as sequences of the optimized clones. The CDRs listed refer to the HuCAL[®] consensus-based antibody gene VH3kappa3.

For example, the affinity of the MS-Roche-7 parental Fab towards Ab1-40 was improved over 35-fold from 1100 nM to 31 nM after L-CDR3 optimization (MS-Roche-7.9) and further improved to 5 nM after H-CDR2 optimization (MS-Roche-7.9H2) as illustrated in Table 3.

The H-CDR2 and L-CDR1 optimization procedure not only increased the affinity but also resulted for some of the clones in a significantly improved staining of amyloid plaques in AD brain section, as particularly seen with MS-Roche 7.9H2 and 7.9H3.

Table 1

Binder name	L-CDR1	pos.49	L-CDR2	pos. 85	L-CDR3	H-CDR1	pos.47	H-CDR2	H-CDR3
MS-Roche #3	RASQSVSSSYLA	Y	GASSRAT	V	QQVYNPPV	GTFESSYAMS	W	AISGSGGTTYADSVKG	LTHARYRYFDV
MS-Roche #3.1	RASQSVSSSYLA	Y	GASSRAT	T	QQVYSVPP	GTFESSYAMS	W	AISGSGGTTYADSVKG	LTHARYRYFDV
MS-Roche #3.2	RASQSVSSSYLA	Y	GASSRAT	V	QQIYSYPP	GTFESSYAMS	W	AISGSGGTTYADSVKG	LTHARYRYFDV
MS-Roche #3.3	RASQSVSSSYLA	Y	GASSRAT	V	HQMSYPP	GTFESSYAMS	W	AISGSGGTTYADSVKG	LTHARYRYFDV
MS-Roche #3.4	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GTFESSYAMS	W	AISGSGGTTYADSVKG	LTHARYRYFDV
MS-Roche #3.5	RASQSVSSSYLA	Y	GASSRAT	T	QQIYDYP	GTFESSYAMS	W	AISGSGGTTYADSVKG	LTHARYRYFDV
MS-Roche #3.6	RASQSVSSSYLA	Y	GASSRAT	V	QQTYNYP	GTFESSYAMS	W	AISGSGGTTYADSVKG	LTHARYRYFDV
MS-Roche #3.2.H1	RASQSVSSSYLA	Y	GASSRAT	V	QQIYSYPP	GTFESSYAMS	W	AISEHGLNIYYADSVKG	LTHARYRYFDV
MS-Roche #3.2.H2	RASQSVSSSYLA	Y	GASSRAT	V	QQIYSYPP	GTFESSYAMS	W	AISQRGQFTYYADSVKG	LTHARYRYFDV
MS-Roche #3.3.H1	RASQSVSSSYLA	Y	GASSRAT	V	HQMSYPP	GTFESSYAMS	W	WISEKRFIYYADSVKG	LTHARYRYFDV
MS-Roche #3.3.H2	RASQSVSSSYLA	Y	GASSRAT	V	HQMSYPP	GTFESSYAMS	W	VISQESQYKYADSVKG	LTHARYRYFDV
MS-Roche #3.3.H3	RASQSVSSSYLA	Y	GASSRAT	V	HQMSYPP	GTFESSYAMS	W	AISQNGFHIYYADSVKG	LTHARYRYFDV
MS-Roche #3.4.H1	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GTFESSYAMS	W	AISETSIRKYYADSVKG	LTHARYRYFDV
MS-Roche #3.4.H2	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GTFESSYAMS	W	VIMVGHITYADSVKG	LTHARYRYFDV
MS-Roche #3.4.H3	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GTFESSYAMS	W	VISQTKRIYYADSVKG	LTHARYRYFDV
MS-Roche #3.4.H4	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GTFESSYAMS	W	AISETGMHIYYADSVKG	LTHARYRYFDV
MS-Roche #3.4.H5	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GTFESSYAMS	W	VISQVGAHIYYADSVKG	LTHARYRYFDV
MS-Roche #3.4.H6	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GTFESSYAMS	W	AISESGWSTYYADSVKG	LTHARYRYFDV
MS-Roche #3.4.H7	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GTFESSYAMS	W	VISETGKNIYYADSVKG	LTHARYRYFDV
MS-Roche #3.4.H8	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GTFESSYAMS	W	AISEHGRFKYYADSVKG	LTHARYRYFDV
MS-Roche #3.4.H9	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GTFESSYAMS	W	AISESSKNIYYADSVKG	LTHARYRYFDV
MS-Roche #3.4.H10	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GTFESSYAMS	W	AISESGRGKYYADSVKG	LTHARYRYFDV
MS-Roche #3.4.H11	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GTFESSYAMS	W	AISEFGKNIYYADSVKG	LTHARYRYFDV
MS-Roche #3.4.H12	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GTFESSYAMS	W	VISQTKQNIYYADSVKG	LTHARYRYFDV
MS-Roche #3.4.H13	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GTFESSYAMS	W	AISEQGRNIYYADSVKG	LTHARYRYFDV
MS-Roche #3.4.H14	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GTFESSYAMS	W	AISESGQYKYADSVKG	LTHARYRYFDV
MS-Roche #3.4.H16	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GTFESSYAMS	W	AISESGVNIYYADSVKG	LTHARYRYFDV
MS-Roche #3.4.H17	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GTFESSYAMS	W	AISEFGQFIYYADSVKG	LTHARYRYFDV
MS-Roche #3.4.H18	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GTFESSYAMS	W	AISQSQSNFIYYADSVKG	LTHARYRYFDV

MS-Roche #3.4.L7	RASQRLRLYL	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISGGSGSTYYADSVKG	LTHYARYRYFV
MS-Roche #3.4.L8	RASQWITKSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISGGSGSTYYADSVKG	LTHYARYRYFV
MS-Roche #3.4.L9	RASRIHVYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISGGSGSTYYADSVKG	LTHYARYRYFV
MS-Roche #3.4.L11	RASQLVGRAYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISGGSGSTYYADSVKG	LTHYARYRYFV
MS-Roche #3.6.H1	RASQSVSSSYLA	Y	GASSRAT	V	QQTYNYPP	GFTFSSYAMS	W	VISEGQYKYADSVKG	LTHYARYRYFV
MS-Roche #3.6.H2	RASQSVSSSYLA	Y	GASSRAT	V	QQTYNYPP	GFTFSSYAMS	W	VISERGINYYADSVKG	LTHYARYRYFV
MS-Roche #3.6.H3	RASQSVSSSYLA	Y	GASSRAT	V	QQTYNYPP	GFTFSSYAMS	W	VISETGKFIYADSVKG	LTHYARYRYFV
MS-Roche #3.6.H4	RASQSVSSSYLA	Y	GASSRAT	V	QQTYNYPP	GFTFSSYAMS	W	AISERGRHIYADSVKG	LTHYARYRYFV
MS-Roche #3.6.H5	RASQSVSSSYLA	Y	GASSRAT	V	QQTYNYPP	GFTFSSYAMS	W	AISESGKTKYADSVKG	LTHYARYRYFV
MS-Roche #3.6.H6	RASQSVSSSYLA	Y	GASSRAT	V	QQTYNYPP	GFTFSSYAMS	W	AISEHGKTIYADSVKG	LTHYARYRYFV
MS-Roche #3.6.H8	RASQSVSSSYLA	Y	GASSRAT	V	QQTYNYPP	GFTFSSYAMS	W	AISEYSKFKYADSVKG	LTHYARYRYFV
MS-Roche #3.6.L1	RASQFIQRFYLA	Y	GASSRAT	V	QQTYNYPP	GFTFSSYAMS	W	AISGGSGSTYYADSVKG	LTHYARYRYFV
MS-Roche #3.6.L2	RASQFLSRYYLA	Y	GASSRAT	V	QQTYNYPP	GFTFSSYAMS	W	AISGGSGSTYYADSVKG	LTHYARYRYFV
MS-Roche #7	RASQSVSSSYLA	Y	GASSRAT	T	FQLYSDPF	GFTFSSYAMS	W	AISGGSGSTYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.1	RASQSVSSSYLA	Y	GASSRAT	V	HQLYSSPY	GFTFSSYAMS	W	AISGGSGSTYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.2	RASQSVSSSYLA	Y	GASSRAT	T	QQIYSFPH	GFTFSSYAMS	W	AISGGSGSTYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.3	RASQSVSSSYLA	Y	GASSRAT	V	HQVYSHPF	GFTFSSYAMS	W	AISGGSGSTYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.4	RASQSVSSSYLA	Y	GASSRAT	V	QQIYNFPH	GFTFSSYAMS	W	AISGGSGSTYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.5	RASQSVSSSYLA	Y	GASSRAT	T	HQVYSSPF	GFTFSSYAMS	W	AISGGSGSTYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.6	RASQSVSSSYLA	Y	GASSRAT	V	HQLYSPPY	GFTFSSYAMS	W	AISGGSGSTYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.7	RASQSVSSSYLA	Y	GASSRAT	T	HQVYSAPF	GFTFSSYAMS	W	AISGGSGSTYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.8	RASQSVSSSYLA	Y	GASSRAT	V	HQVYSFPI	GFTFSSYAMS	W	AISGGSGSTYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.9	RASQSVSSSYLA	Y	GASSRAT	T	LQIYNMPI	GFTFSSYAMS	W	AISGGSGSTYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.10	RASQSVSSSYLA	Y	GASSRAT	T	QQVYNPPH	GFTFSSYAMS	W	AISGGSGSTYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.11	RASQSVSSSYLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	AISGGSGSTYYADSVKG	GKGNTHKPYGVRYF DV

MS-Roche #7.12	RASQVWSSPYLA	S	GSSNRAT	V	LQLYNIPN	GTFSSYGMS	W	NISSGSGSTYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.13	RASQSVSSSYLA	Y	GASSRAT	V	HQVYSPPF	GTFSSYAMS	W	AISGSGSTYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.2.H1	RASQSVSSSYLA	Y	GASSRAT	T	QQIYSFPH	GTFSSYAMS	W	AINANGLKYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.2.H2	RASQSVSSSYLA	Y	GASSRAT	T	QQIYSFPH	GTFSSYAMS	W	AINGTGMKKYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.2.H3	RASQSVSSSYLA	Y	GASSRAT	T	QQIYSFPH	GTFSSYAMS	W	AINANGYKTYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.2.H4	RASQSVSSSYLA	Y	GASSRAT	T	QQIYSFPH	GTFSSYAMS	W	AINSKGSRYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.2.H5	RASQSVSSSYLA	Y	GASSRAT	T	QQIYSFPH	GTFSSYAMS	W	AINATGRSKYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.2.H6	RASQSVSSSYLA	Y	GASSRAT	T	QQIYSFPH	GTFSSYAMS	W	AINARGNRTYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.2.H7	RASQSVSSSYLA	Y	GASSRAT	T	QQIYSFPH	GTFSSYAMS	W	AINSRGSDTHYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.2.H8	RASQSVSSSYLA	Y	GASSRAT	T	QQIYSFPH	GTFSSYAMS	W	AINASGHKTYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.2.L1	RASQVYDRTYLA	Y	GASSRAT	T	QQIYSFPH	GTFSSYAMS	W	AISGSGSTYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.2.L2	RASQYISFRYLA	Y	GASSRAT	T	QQIYSFPH	GTFSSYAMS	W	AISGSGSTYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.2.L4	RASQFIRRSYLA	Y	GASSRAT	T	QQIYSFPH	GTFSSYAMS	W	AISGSGSTYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.3.H1	RASQSVSSSYLA	Y	GASSRAT	V	HQVYSHPF	GTFSSYAMS	W	AISAINKTYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.3.L1	RASQYLHYGYLA	Y	GASSRAT	V	HQVYSHPF	GTFSSYAMS	W	AISGSGSTYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.4.H1	RASQSVSSSYLA	Y	GASSRAT	V	QQIYNFPH	GTFSSYAMS	W	AINATGYRTYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.4.H2	RASQSVSSSYLA	Y	GASSRAT	V	QQIYNFPH	GTFSSYAMS	W	AINYNGARIYYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.9.H1	RASQSVSSSYLA	Y	GASSRAT	T	LQIYNMPI	GTFSSYAMS	W	AINANGQRKFYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.9.H2	RASQSVSSSYLA	Y	GASSRAT	T	LQIYNMPI	GTFSSYAMS	W	AINADGNRKYADSVKG	GKGNTHKPYGVRYF DV
MS-Roche #7.9.H3	RASQSVSSSYLA	Y	GASSRAT	T	LQIYNMPI	GTFSSYAMS	W	AINYQGNRKYADSVKG	GKGNTHKPYGVRYF DV

MS-Roche #7.9.H4	RASQSVSSSYLA	Y	GASSRAT	T	LQIYNMPI	GFTFSSYAMS	W	AINAVGMKFFYADSVKG	GKGNTHKPYGVVRYF DV
MS-Roche #7.9.H5	RASQSVSSSYLA	Y	GASSRAT	T	LQIYNMPI	GFTFSSYAMS	W	AINHAGNKYYADSVKG	GKGNTHKPYGVVRYF DV
MS-Roche #7.9.L1	RASQRLSPRYLA	Y	GASSRAT	T	LQIYNMPI	GFTFSSYAMS	W	AISGSGSSTYYADSVKG	GKGNTHKPYGVVRYF DV
MS-Roche #7.9.L.2	RASQYLHKRYLA	Y	GASSRAT	T	LQIYNMPI	GFTFSSYAMS	W	AISGSGSSTYYADSVKG	GKGNTHKPYGVVRYF DV
MS-Roche #7.9.H6	RASQSVSSSYLA	Y	GASSRAT	T	QQIYSFPH	GFTFSSYAMS	W	AINARGNRTYYADSVKG	GKGNTHKPYGVVRYF DV
MS-Roche #7.9.H7	RASQSVSSSYLA	Y	GASSRAT	T	LQIYNMPI	GFTFSSYAMS	W	AINASGTRTYADSVKG	GKGNTHKPYGVVRYF DV
MS-Roche #7.9.H8	RASQSVSSSYLA	Y	GASSRAT	T	LQIYNMPI	GFTFSSYAMS	W	AINASGSKIYYADSVKG	GKGNTHKPYGVVRYF DV
MS-Roche #7.9.H9	RASQSVSSSYLA	Y	GASSRAT	T	LQIYNMPI	GFTFSSYAMS	W	AINAGKGNKYYADSVKG	GKGNTHKPYGVVRYF DV
MS-Roche #7.11.H1	RASQSVSSSYLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	GINAAGFRTYYADSVKG	GKGNTHKPYGVVRYF DV
MS-Roche #7.11.H2	RASQSVSSSYLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	AINANGYKYYADSVKG	GKGNTHKPYGVVRYF DV
MS-Roche #7.11.H3	RASQSVSSSYLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	GINANGNRTYYADSVKG	GKGNTHKPYGVVRYF DV
MS-Roche #7.11.H4	RASQSVSSSYLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	AINANGYKTYADSVKG	GKGNTHKPYGVVRYF DV
MS-Roche #7.11.H5	RASQSVSSSYLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	AINAHGQRTYYADSVKG	GKGNTHKPYGVVRYF DV
MS-Roche #7.11.L1	RASQRLRYLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	AISGSGSSTYYADSVKG	GKGNTHKPYGVVRYF DV
MS-Roche #7.12.H1	RASQVVFRRYLA	S	GSSNRAT	V	LQLYNIPN	GFTFSSYGMS	W	NINGNKNRKYADSVKG	GKGNTHKPYGVVRYF DV
MS-Roche #7.12.L1	RASQVVFRRYLA	S	GSSNRAT	V	LQLYNIPN	GFTFSSYGMS	W	NISGSGSSTYYADSVKG	GKGNTHKPYGVVRYF DV
MS-Roche #7.12.L2	RASQRFYKYLA	S	GSSNRAT	V	LQLYNIPN	GFTFSSYGMS	W	NISGSGSSTYYADSVKG	GKGNTHKPYGVVRYF DV
MS-Roche #7.12.L3	RASQFVRRGFLA	S	GSSNRAT	V	LQLYNIPN	GFTFSSYGMS	W	NISGSGSSTYYADSVKG	GKGNTHKPYGVVRYF DV
MS-Roche #7.12.L4	RASQRLKRSYLA	S	GSSNRAT	V	LQLYNIPN	GFTFSSYGMS	W	NISGSGSSTYYADSVKG	GKGNTHKPYGVVRYF DV
MS-Roche #7.12.L5	RASQRLKRSYLA	S	GSSNRAT	V	LQLYNIPN	GFTFSSYGMS	W	NISGSGSSTYYADSVKG	GKGNTHKPYGVVRYF DV

MS-Roche #7.12.L6	RASQYLWYRYLA	S	GSSNRAT	V	LQLYNIPN	GFTFSSYGMS	W	NISGSGSSTYYADSVKG	DV	GKGNTHKPYGYVRVF
MS-Roche #7.12.L7	RASQWIRKTYLA	S	GSSNRAT	V	LQLYNIPN	GFTFSSYGMS	W	NISGSGSSTYYADSVKG	DV	GKGNTHKPYGYVRVF
MS-Roche #8	RASQSVSSSYLA	Y	GASSRAT	T	QQLSSFPP	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	LLSRGYN	GYHHKFDV
MS-Roche #8.1	RASQSVSSSYLA	Y	GASSRAT	T	QQLSNYPP	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	LLSRGYN	GYHHKFDV
MS-Roche #8.2	RASQSVSSSYLA	Y	GASSRAT	T	QQLSSYPP	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	LLSRGYN	GYHHKFDV
MS-Roche #8.1.H1	RASQSVSSSYLA	Y	GASSRAT	T	QQLSNYPP	GFTFSSYAMS	W	AISRSGSNIYYADSVKG	LLSRGYN	GYHHKFDV
MS-Roche #8.2.H1	RASQSVSSSYLA	Y	GASSRAT	T	QQLSSYPP	GFTFSSYAMS	W	AISITGRRKYYADSVKG	LLSRGYN	GYHHKFDV
MS-Roche #8.2.H2	RASQSVSSSYLA	Y	GASSRAT	T	QQLSSYPP	GFTFSSYAMS	W	AISRTGSKTYADSVKG	LLSRGYN	GYHHKFDV
MS-Roche #8.2.H4	RASQSVSSSYLA	Y	GASSRAT	T	QQLSSYPP	GFTFSSYAMS	W	ATSVKGKTYADSVKG	LLSRGYN	GYHHKFDV
MS-Roche #8.2.L1	RASQRVSGRYLA	Y	GASSRAT	T	QQLSSYPP	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	LLSRGYN	GYHHKFDV

Sequences belonging to V_H3 and V_K3 HuCAL consensus sequences see Figure 1 A

Example 6

Construction of HuCAL[®] immunoglobulin expression vectors

Heavy chain cloning. The multiple cloning site of pcDNA3.1+ (Invitrogen) was removed (*NheI/ApaI*), and a stuffer compatible with the restriction sites used for HuCAL[®] design was inserted for the ligation of the leader sequences (*NheI/EcoRI*), VH-domains (*MunI*), and the immunoglobulin constant regions (*BlnI/ApaI*). The leader sequence (EMBL 83133) was equipped with a Kozak sequence (Kozak, 1987). The constant regions of human IgG (PIR A02146), IgG4 (EMBL K01316), and serum IgA1 (EMBL J00220) were dissected into overlapping oligonucleotides with length of about 70 bases. Silent mutations were introduced to remove restriction sites non-compatible with the HuCAL[®] design. The oligonucleotides were spliced by overlap extension-PCR.

During sub-cloning from Fab into IgG, the VH DNA sequence of the Fab is cut out via *MfeI* / *BlnI* and ligated into the IgG vector opened via *EcoRI* / *BlnI*. *EcoRI* (*g/aattc*) and *MfeI* (*c/aattg*) share compatible cohesive ends (*aatt*) and the DNA sequence of the original *MfeI* site in the Fab changes from: *c/aattg* to: *g/aattg* after ligation into the IgG expression vector, thereby destroying both *MfeI* and *EcoRI* site, and thus also leading to an amino acid change from Q (codon: *caa*) to E (codon: *gaa*).

Light chain cloning. The multiple cloning site of pcDNA3.1/Zeo+ (Invitrogen) was replaced by two different stuffers. The κ -stuffer provided restriction sites for insertion of a κ -leader (*NheI/EcoRV*), HuCAL[®]-scFv V κ -domains (*EcoRV/BsiWI*), and the κ -chain constant region (*BsiWI/ApaI*). The corresponding restriction sites in the λ -stuffer were *NheI/EcoRV* (λ -leader), *EcoRV/HpaI* (V λ -domains), and *HpaI/ApaI* (λ -chain constant region). The κ -leader (EMBL Z00022) as well as the λ -leader (EMBL J00241) were both equipped with Kozak sequences. The constant regions of the human κ - (EMBL L00241) and λ -chain (EMBL M18645) were assembled by overlap extension-PCR as described above.

Generation of IgG-expressing CHO-cells. CHO-K1 cells were co-transfected with an equimolar mixture of IgG heavy and light chain expression vectors. Double-resistant

transfectants were selected with 600 µg/ml G418 and 300 µg/ml Zeocin (Invitrogen) followed by limiting dilution. The supernatant of single clones was assessed for IgG expression by capture-ELISA. Positive clones were expanded in RPMI-1640 medium supplemented with 10% ultra-low IgG-FCS (Life Technologies). After adjusting the pH of the supernatant to 8.0 and sterile filtration, the solution was subjected to standard protein A column chromatography (Poros 20 A, PE Biosystems).

Example 7: Pepspot analysis with decapeptides

The following aminoacid sequence encompassing Aβ (1-42) was divided into 43 overlapping decapeptides with a frameshift of 1 aminoacid.

ISEVKM¹DAEF RHDSGYEVHH QKLVFFAEDV GSNKGAIIGL MVGGVVI⁴²ATV IV (SEQ ID NO: 414). Accordingly, DAEF RHDSGYEVHH QKLVFFAEDV GSNKGAIIGL MVGGVVIA (SEQ ID NO: 27) as enclosed represents amino acids 1 to 42 of Aβ4/β-A4 peptide.

The 43 decapeptides were synthesized with N-terminal acetylation and C-terminal covalent attachment to a cellulose sheet ("pepspot") by a commercial supplier (Jerini BioTools, Berlin). The cellulose sheet is incubated for 2 hours on a rocking platform with monoclonal antibody (2 µg/ml) in blocking buffer (50 mM Tris·HCl, 140 mM NaCl, 5 mM NaEDTA, 0.05% NP40 (Fluka), 0.25% gelatine (Sigma), 1% bovine serum albumine fraction V (Sigma), pH 7.4). The sheet is washed 3 times 3 minutes on a rocking platform with TBS (10 mM Tris·HCl, 150 mM NaCl, pH 7.5). It is then wetted with cathode buffer (25 mM Tris base, 40 mM 6-Aminohexane acid, 0.01% SDS, 20% methanol) and transferred to a semi-dry blotting stack with the peptide side facing a PVDF membrane (Biorad) of equal size.

The semi-dry blotting stack consists out of freshly wetted filter papers (Whatman No.3) slightly larger than the peptide sheet:

3 papers wetted with Cathode buffer

the peptide sheet

a sheet of PVDF membrane wetted with methanol

3 papers wetted with Anode buffer 1 (30mM Tris base, 20% methanol)

3 papers wetted with Anode buffer 2 (0.3 mM Tris base, 20% methanol)

The transfer is conducted at a current density between Cathode and Anode of 0.8 mA/cm² for 40 minutes which is sufficient to elute most of the antibody from the cellulose sheet and deposit it on the PVDF membrane. The PVDF membrane is then exchanged for a 2nd PVDF membrane and transferred for another 40 minutes to ensure complete elution from the cellulose sheet.

The PVDF membrane is immersed in blocking buffer for 10 minutes. Then HRP-labeled anti-human Ig H+L (Pierce) is added at 1:1000 dilution and the membrane is incubated on a rocking platform for 1 hour. It is washed 3x10 minutes with TBST (TBS with 0.005% Tween20) . Color is developed by immersing the membrane into a solution made of 3 mg 4-chloronaphthol dissolved in 9 ml methanol with 41 ml PBS (20 mM Na-phosphate, 150 mM NaCl, pH 7.2) an 10 µl 30% hydrogen peroxide (Merck). After the development of blue-black spots the membrane is washed extensively with water and dried.

The assignment of antibody-reactive pepspots is made by visual inspection through a transparent spot matrix. The epitopes of the antibody in question is defined as the minimal aminoacid sequence in reactive peptides. For comparison mouse monoclonal antibodies (BAP-2, BAP-1, BAP-17 BAP-21, BAP-24, and 4G8) are analyzed in the same way, except using HRP-labeled anti-mouse Ig instead of anti-human Ig.

It is of note that affinity maturation and conversion of the monovalent Fab fragments into full-length IgG1 antibodies results usually in some broadening of the epitope recognition sequence as indicated by pepspot and ELISA analyses. This may be related to the recruitment of more contact points in the antibody-antigen interaction area as a consequence of the affinity maturation or to a stronger binding to the minimal epitope such that also weak interactions with adjacent amino acid can be detected. The latter may be the case when Aβ-derived peptides are probed with full-length IgG antibodies. As illustrated in Table 2 for the pepspot analysis, the recognition sequences of the N-terminal and middle epitopes are extended by up to three amino acids when parent Fabs and corresponding fully matured IgG antibodies are compared. However, it has to be kept in mind that the decapeptides are modified for covalent attachment at the C-terminal amino acid and this amino acid may therefore not easily be accessible to the full-length antibody due to steric

hindrance. If this is the case the last C-terminal amino acid does not significantly contribute to the epitope recognition sequence and a potential reduction of the minimal recognition sequence by one amino acid at the C-terminal end has to be considered in the pepspot analysis as used in the present invention.

antibody	position	position
MSR-3 Fab	3-4	18-23
MSR-7 Fab	3-5	19-24
MSR-8 Fab	4-5	18-21
MSR-9 Fab	(1)3-9	18-24
MSR-10 Fab	(4-10)	19-20
MSR-11 Fab	3-7	(18-20)
MSR-26 Fab	3-5	(16)-19-23
MSR-27 Fab	(3)6-9	13-18(20)
MSR-29 Fab		14-16(20)
MSR-37 Fab	(4-6)	(19-24)
MSR-41 Fab	3-7	(17-21)
MSR-42 Fab	(4-9)	(18-24)
MSR 3.4.H7 IgG1	1-3	19-26
MSR 7.9.H2 IgG1	1-4	19-24
MSR 7.9.H7 IgG1	4-6	19-26
MSR 7.2.H2x7.2.L1 IgG1	(1-4) 5-9	18-26
MSR 7.11.H1x7.2.L1 IgG1	4-6	19-26
BAP-2	4-6	
4G8		19-20(23)
BAP-21		32-34
BAP-24		38-40
BAP-1	4-6	
BAP-17		38-40

Table 2: Pepspot analysis of binding Fabs and full-length IgG antibodies to decapeptides on a cellulose sheet. The numbers refer to the essential amino acids from the A β 1-40 sequence which have to be present in the decapeptide for optimal binding of antibody. A weak peptide reactivity, and hence a weak contribution to the epitope, is indicated by brackets.

Example 8: Determination of K_D values for MS-R Fab and MS-R IgG1 antibody binding to A β 1-40 and A β 1-42 fibers *in vitro* by surface plasmon resonance (SPR)

Binding of anti-A β antibodies (Fabs and IgG1) to fibrillar A β was measured online by surface plasmon resonance (SPR), and the affinities of the molecular interactions were determined as described by Johnson, *Anal. Biochem.* 1991, 198, 268 – 277, and Richalet-Sécordel, *Anal. Biochem.* 1997, 249, 165 – 173. Biacore2000 and Biacore3000 instruments were used for these measurements. A β 1-40 and A β 1-42 fibers were generated *in vitro* by incubation of synthetic peptides at a concentration of 200 μ g/ml in 10 mM Na-acetat buffer (pH 4.0) for three days at 37°C. Electron microscopic analysis confirmed a fibrillar structure for both peptides, A β 1-40 showing predominantly shorter (< 1 micron) and A β 1-42 predominantly longer (> 1 micron) fibers. These fibers are assumed to represent aggregated A β peptides in human AD brain more closely than ill-defined mixtures of amorphous aggregates and unstructured precipitates. The fibers were diluted 1:10 and directly coupled to a "Pioneer Sensor Chip F1" as described in the Instruction Manual of the manufacturer (BIAapplication Handbook, version AB, Biacore AB, Uppsala, 1998). In initial experiments it was found that selected MS-Roche Fabs differed substantially in their reaction kinetics and therefore the mode of data analysis had to be chosen accordingly. For binders with slow kinetics K_D values were calculated by curve fitting of the time-dependent sensor responses, i. e. from the ratio of k_{off}/k_{on} . Binders with fast kinetics were analyzed by fitting the concentration-dependent sensor responses at equilibrium (adsorption-isotherms). K_D values were calculated from the Biacore sensograms based on the total Fab concentration as determined by a protein assay. For the clones derived from the 1st and 2nd affinity maturation cycle the content of

active Fab in each preparation was determined in the Biacore according to a method described by Christensen, *Analytical Biochemistry* (1997) 249, 153 –164. Briefly, time-dependent protein binding to A β 1-40 fibers immobilized on the Biacore chip was measured during the association phase under mass-limited conditions at different flow rates of the analyte solution. The conditions of mass limitation were realized by immobilizing high amounts of A β fibers (2300 response units) on the chip surface of a measuring channel and by working at relatively low analyte concentrations, i. e. 160 nM (based on the total Fab protein concentration).

A summary of the K_D values of selected MS-Roche clones identified in the primary screen of the HuCAL library and their corresponding matured derivatives after the 1st and 2nd affinity maturation cycle is shown in Table 3. In the 1st affinity maturation cycle the heavy chain CDR3 (VH-CDR3) was kept constant and optimization was focussed on diversification of the light chain CDR3 (VL-CDR3). In the 2nd affinity cycle diversification of VL-CDR1 and VH-CDR2 was performed. Some of the binders from the 1st maturation cycle were converted to full-length human IgG1 antibodies according to the technology developed by MorphoSys as described in Example 6 and K_D values determined in the Biacore as described above. The K_D values for full-length IgG1 binding to A β 1-40 and A β 1-42 fibers are shown in Table 4.

Matured derivatives from both the L-CDR1 as well as H-CDR2 library after the 2nd maturation cycle were identified and allowed combination of light and heavy chains. The cross-cloning strategy is described in Example 13. Either whole light chains, LCDR1 or L-CDR1+2 were exchanged. K_D values of selected cross-cloned Fabs are shown in Table 8.

Some of the Fabs from the 1st and 2nd maturation cycles and from the cross-cloned binders were converted to full-length human IgG1 antibodies according to the technology developed by MorphoSys as described in Example 6. K_D values of IgG binding to A β 1-40 and A β 1-42 fibers were determined in the Biacore. Briefly, a kinetic model for the stepwise formation of a bivalent complex was used, and K_D values were calculated by Scatchard type analysis of equilibrium binding. Due to the very slow association process at low antibody concentration (several hours to reach equilibrium) equilibrium binding data were obtained by extrapolation of the association curves to long time intervals. The on- and off rates for the formation of

the monovalent and bivalent complex were determined via the curve fit procedure and used for the extrapolation. Based on these R_{eq} values a Scatchard analysis was performed and K_D values for the formation of the monovalent and the bivalent complex were determined. The data are summarized in Table 5. From the curvilinear Scatchard plot a higher (bivalent) and lower (monovalent) affinity interaction was derived for the MS-R IgGs derived from the 2nd affinity maturation cycle and cross-clones. These two affinities represent the lower and upper K_D values of the range indicated in Table 5.

76

Secreted clones from	MS-R#	K _D Aβ ₁₋₄₀ nM	K _D Aβ ₁₋₄₂ nM	MS-R#	K _D Aβ ₁₋₄₀ nM	K _D Aβ ₁₋₄₂ nM	MS-R#	K _D Aβ ₁₋₄₀ nM	K _D Aβ ₁₋₄₂ nM
primary screen	3	930	1300	7	1100	1714	8	850	1000
1 st affinity maturation	3.2	52	240	7.2	22	58	8.1	24	42
	3.3	38	104	7.3	23	88	8.2	24	64
	3.4	32	103	7.4	28	103			
	3.6	40	68	7.9	31	93			
				7.11	22	74			
				7.12	28	60			
2 nd affinity maturation	3.2H1	4.4	3.3	7.2H1	9.3	10.2	8.1H1	13.6	9.2
	3.2H2	5.2	1.1	7.2H2	8.2	8.2	8.2H1	1.6 ^a	2.1 ^a
	3.3H1	17.1	19.4	7.2H3	45.4	5.3	8.2H3	n.d.	3.1
	3.3H2	10.6	22.8	7.2H4	5.9	5.0	8.2H4	12.1	11.9
	3.3H3	1.4	3.3	7.2H5	8.0	10.1	8.2L1	4.8	3.7
	3.4H1	13.5	14.0	7.2H6	1.0	n.d.			
	3.4H3	6.7	8.4	7.2H7	15.5	8.1			
	3.4H4	33.0	43.0	7.2H8	1.5	2.1			
	3.4H5	26.5	36.0	7.2L1	13.3	12.7			
	3.4H6	49.0	60.0	7.2L2	5.6	4.0			
	3.4H7	19.2	31.7	7.2L4	1.1	1.1			
	3.4H8	10.7	26.5	7.3H1	8.0	11.2			
	3.4H9	21.7	18.6	7.3L1	4.5	6.0			
	3.4H10	8.1	10.1	7.4H1	8.0	6.6			
	3.4H11	19.5	8.3	7.4H2	9.9	6.2			
	3.4H12	25.5	27.0	7.9H1	4.9	5.4			
	3.4H13	32.3	18.8	7.9H2	5.0	5.7			
	3.4H14	13.3	16.8	7.9H3	4.2	2.8			
	3.4H16	25.5	15.6	7.9H4	4.8	4.2			
	3.4H17	2.0	4.3	7.9H5	1.7	1.8			
	3.4H18	17.1	10.0	7.9H6	1.2	1.2			
	3.4L7	9.3	9.3	7.9H7	1.0	0.9			
	3.4L8	6.2	13.0	7.9H8	0.8	0.7			
	3.4L9	16.3	9.1	7.9H9	0.9	0.9			
	3.4L11	5.3	2.6	7.9L1	1.0	1.1			
	3.6H1	18.9	23.1	7.9L2	1.0	0.5			
	3.6H2	19.8	54.0	7.11H1	12.7	6.7			
	3.6H3	5.4	7.5	7.11H2	0.3	0.3			
	3.6H4	13.0	7.8	7.11H3	6.6	4.4			
	3.6H5	8.2	6.0	7.11H4	1.0	1.7			
	3.6H6	36.0	11.8	7.11H5	3.4	1.7			
	3.6H8	2.5	2.5	7.11L1	1.1	1.2			
	3.6L1	15.6	11.1	7.12H1	0.6	0.8			
	3.6L2	13.7	13.1	7.12L1	n.d.	3.8			
				7.12L2	4.0	5.4			
				7.12L3	0.8	0.9			
				7.12L4	2.0	0.6			
				7.12L5	0.8	0.6			
				7.12L6	n.d.	n.d.			
				7.12L7	n.d.	n.d.			

Table 3

Table 3: K_D values for MS-R Fab binding to A β 1-40 and A β 1-42 fibers as determined in the Biacore. For the clones derived from the 1st and 2nd affinity maturation cycle the values are corrected for the content of active Fab present in each sample as described in the text. ^a, values were calculated from the concentration-dependent sensor responses at equilibrium; n.d., not determined.

Table 4:

MS-R #	K_D A β ₁₋₄₀ nM	K_D A β ₁₋₄₂ nM
3.3 IgG1	3.7	6.6
7.11 IgG1	2.3	5.7
7.12 IgG1	3.1	13.7
8.1 IgG1	6.6	12.3

Table 4: K_D values for MS-R IgG1 binding to A β 1-40 and A β 1-42 fibers as determined in the Biacore. The IgGs were derived from MS-R Fabs selected after the 1st affinity maturation cycle. The values are corrected for the content of active MS-R IgGs present in each sample as described in the text.

<i>Selected clones from</i>	MS-R IgG1	K_D Aβ₁₋₄₀ <i>nM</i>	K_D Aβ₁₋₄₂ <i>nM</i>
<i>1st affinity maturation</i>	3.3	3.7	6.6
	7.11	2.3	5.7
	7.12	3.1	13.7
	8.1	6.6	12.3
<i>2nd affinity maturation</i>	3.4.H7	0.10-0.30	0.10-0.30
	7.2.H4	0.09-0.30	0.10-0.66
	7.9.H2	0.12-0.42	0.11-0.38
	7.9.H3	0.10-0.50	0.10-0.40
	7.9.H7	0.25-0.69	0.24-0.70
	7.12.L1	1.20-3.50	0.74-2.90
	8.2.H2	0.16-1.00	0.12-0.92
<i>cross-cloned Fabs</i>	3.6.H5x3.6.L2	0.20-1.03	0.20-0.95
	3.6.H8x3.6.L2	0.22-0.95	0.22-0.82
	7.4.H2x7.2.L1	0.12-0.63	0.12-0.56
	7.11.H1x7.2.L1	0.14-0.66	0.15-0.67
	7.11.H1x7.11.L1	0.11-0.70	0.13-0.70

Table 5: K_D values for MS-R IgG1 binding to Aβ₁₋₄₀ and Aβ₁₋₄₂ fibers as determined in the Biacore. The IgGs were derived from MS-R Fabs selected after the 1st and 2nd affinity maturation cycle and from crosscloned Fabs. The values are corrected for the content of active MS-R IgGs present in each sample as described in the text. The two K_D values given for MS-R IgGs derived from the 2nd affinity maturation step and cross-cloned binders represent higher and lower affinity interaction as calculated from the curvilinear Scatchard plots. With a number of additional MS-R IgGs (for example MS-R IgG 7.9.H2x7.12.L2 and MS-R IgG 7.9.H4x7.12.L2), complex curvilinear Scatchard blots were obtained and determination of K_D-values was therefore not possible.

Example 9: Staining of genuine human amyloid plaques in brain sections of an Alzheimer's Disease patient by indirect immunofluorescence

Selected MS-Roche Fabs and full-length IgG1 were tested for binding to β -amyloid plaques by immunohistochemistry analysis. Cryostat sections of unfixed tissue from human temporal cortex (obtained postmortem from a patient that was positively diagnosed for Alzheimer's disease) were labeled by indirect immunofluorescence using MS-Roche Fabs or full-length human IgG1 antibodies at various concentrations. Fabs and IgG1 antibodies were revealed by goat anti-human affinity-purified F(ab')₂ fragment conjugated to Cy3 and goat anti-human (H+L) conjugated to Cy3, respectively. Both secondary reagents were obtained from Jackson Immuno Research. Controls included an unrelated Fab and the secondary antibodies alone, which all gave negative results. Typical examples of plaque stainings with selected MS-Roche Fabs and MS-Roche IgG1 antibodies are shown in Figures 5 to 7.

Example 10: Polymerization Assay: Prevention of A β aggregation

Synthetic A β when incubated in aqueous buffer over several days spontaneously aggregates and forms fibrillar structures which are similar to those seen in amyloid deposits in the brains of Alzheimer's Disease patients. We have developed an *in vitro* assay to measure incorporation of biotinylated A β into preformed A β aggregates in order to analyze the A β -neutralizing potential of anti-A β antibodies and other A β -binding proteins such as albumin (Bohrmann et al., 1999, J. Biol. Chem. 274, 15990-15995). The effect of small molecules on A β aggregation can also be analyzed in this assay.

Experimental procedure:

NUNC Maxisorb microtiter plates (MTP) are coated with a 1:1 mixture of A β 1-40 and A β 1-42 (2 μ M each, 100 μ l per well) at 37°C for three days. Under these conditions highly aggregated, fibrillar A β is adsorbed and immobilized on the surface of the well. The coating solution is then removed and the plates are dried at room temperature for 2-4 hours. (The dried plates can be stored at -20°C). Residual binding sites are blocked by adding 300 μ l/well phosphate-buffered saline containing 0.05 % Tween 20 (T-PBS) and 1 % bovine serum albumin (BSA). After 1-2 hours incubation at room temperature the plates are washed 1 x with 300 μ l T-PBS. A

solution of 20 nM biotinylated A β 1-40 in 20 mM Tris-HCl, 150 mM NaCl pH 7.2 (TBS) containing 0.05 % NaN₃ and serially diluted antibody is added (100 μ l/well) and the plate incubated at 37°C overnight. After washing 3 x with 300 μ l T-PBS a streptavidin-POD conjugate (Roche Molecular Biochemicals), diluted 1:1000 in T-PBS containing 1% BSA, is added (100 μ l/well) and incubated at room temperature for 2 hours. The wells are washed 3 x with T-PBS and 100 μ l/well of a freshly prepared tetramethyl-benzidine (TMB) solution are added. [Preparation of the TMB solution: 10 ml 30 mM citric acid pH 4.1 (adjusted with KOH) + 0.5 ml TMB (12 mg TMB in 1 ml acetone + 9 ml methanol) + 0.01 ml 35 % H₂O₂]. The reaction is stopped by adding 100 μ l/well 1 N H₂SO₄ and absorbance is read at 450 nm in a microtiter plate reader.

Result:

Figure 8 shows that MS-Roche IgG1 antibodies prevented incorporation of biotinylated A β 1-40 into preformed A β 1-40/A β 1-42 aggregates. The A β -neutralizing capacity of these full-length human IgGs was similar to that of the mouse monoclonal antibody BAP-1 which had been generated by a standard immunization procedure and specifically recognizes amino acid residues 4-6 of the A β peptide when analyzed by the Pepspot technique as described in example 7. Mouse monoclonal antibody BAP-2 which also reacts exclusively with amino acids 4-6 (Brockhaus, unpublished) was significantly less active in this assay. An even lower activity was found with the A β 1-40 C-terminal specific antibody BAP-17 (Brockhaus, Neuroreport 9 (1998), 1481-1486) and the monoclonal antibody 4G8 which recognizes an epitope between position 17 and 24 in the A β sequence (Kim, 1988, Neuroscience Research Communication Vol. 2, 121-130). BSA at a concentration of up to 10 μ g/ml did not affect incorporation of biotinylated A β and served as a negative control. However, at higher concentrations, i. e. > 100 μ g/ml, BSA has been reported to inhibit binding of biotinylated A β into preformed A β fibers (Bohrmann, (1999) *J Biol Chem* 274 (23), 15990-5) indicating that the interaction of BSA with A β is not of high affinity.

Example 11: De-polymerization Assay: Release of biotinylated A β from aggregated A β

In a similar experimental setup we have tested the potential of MS-Roche IgG antibodies to induce depolymerization of aggregated A β . Biotinylated A β 1-40 was first incorporated into preformed A β 1-40/A β 1-42 fibers before treatment with various anti-A β antibodies. Liberation of biotinylated A β was measured using the same assay as described in the polymerization assay.

Experimental procedure:

NUNC Maxisorb microtiter plates (MTP) are coated with a 1:1 mixture of A β 1-40 and A β 1-42 as described in the polymerization assay. For incorporation of biotinylated A β the coated plates are incubated with 200 μ l/well 20 nM biotinylated A β 1-40 in TBS containing 0.05 % NaN₃ at 37°C overnight. After washing the plate with 3 x 300 μ l/well T-PBS, antibodies serially diluted in TBS containing 0.05 % NaN₃ were added and incubated at 37°C for 3 hours. The plate was washed and analyzed for the presence of biotinylated A β 1-40 as described above.

Result:

Figures 9A to D shows that the inventive antibodies induced de-polymerization of aggregated A β as measured by the release of incorporated biotinylated A β 1-40. The MS-R antibodies and the mouse monoclonal antibody BAP-1 were similarly active whereas the BAP-2, BAP-17 and 4G8 antibodies were clearly less efficient in liberating biotinylated A β from the bulk of immobilized A β aggregates. BAP-1 can clearly be differentiated from the MS-R antibodies by its reactivity with cell surface full-length APP (see Figure 15), and antibodies like BAP-1 with such properties are not useful for therapeutic applications as potential autoimmunological reactions may be induced. It is interesting to note that BAP-2, despite its specificity for amino acid residue 4-6 which is exposed in aggregated A β has a clearly lower activity in this assay indicating that not all N-terminus specific antibodies a priori are equally efficient in releasing A β from preformed aggregates. The MS-Roche IgGs are clearly superior to BAP-2 with respect to the depolymerizing activity. The relatively low

efficiency of BAP-17 (C-terminus-specific) and 4G8 (amino acid residues 16-24-specific) in this assay is due to the cryptic nature of these two epitopes in aggregated A β . As already noted in the polymerization assay, BSA at the concentrations used here had no effect on aggregated A β .

The MS-R antibodies derived from the 2nd affinity maturation cycle and from the cross-cloned binders show in general a higher efficacy in the de-polymerization assay (comparison of figure 9A with figures 9B and C), which is consistent with the increased binding affinity of these antibodies (see tables 3-5). The monoclonal antibodies AMY-33 and 6F/3D have been reported to prevent A β aggregation in vitro under certain experimental conditions (Solomon, (1996) Proc. Natl. Acad. Sci. USA 93, 452-455; AMY-33 and 6F/3D antibodies were obtained from Zymed Laboratories Inc., San Francisco (Order No. 13-0100) and Dako Diagnostics AG, Zug, Switzerland (Order No. M087201), respectively). As demonstrated in figure 9D both of these antibodies were completely inactive in the de-polymerization assay.

EXAMPLE 12: Epitope analysis by ELISA on peptide conjugates.

The following heptapeptides (single letter code) were obtained by solid-phase synthesis and purified by liquid chromatography using the techniques known in the art.

AEFRHDC
EFRHDSC
FRHDSGC
RHDSGYC
HDSGYEC
DSGYEVC
SGYEVHC
YEVHHQC
EVHHQKC
VHHQKLC
HHQKLVC
HQKLVFC
QKLVFFC
KLVFFAC
LVFFAEC
VFFAEDC

FFAEDVC
FAEDVGC
AEDVGSC
EDVGSNC
DVGSNKC
VGSNKGK
GSNKGAC
CSNKGAI
CNKGAI
CKGAIIG
CGLMVGG
CMVGGVV
CGGVVIA

The peptides were dissolved in DMSO to arrive at 10 mM concentration.

Bovine Albumin (essentially fatty acid free BSA , Sigma Lot 112F-9390) was dissolved to 10 mg/ml in 0.1M sodium bicarbonate and activated by addition per ml of 50 µl of a 26 mg/ml solution of N-succinimidyl-maleinimido propionate (NSMP, Pierce) in DMSO. After 15 minutes reaction at room temperature the activated BSA was purified by gel filtration (NAP-10, Pharmacia) in PBS with 0.1% sodium azide as solvent. 50 µl of NSMP activated BSA (6.7 mg/ml) was diluted with 50 µl of PBS, 0.1% sodium azide and 10 µl of peptide solution (1 mM in DMSO) was added. As negative control activated BSA was mock-treated without peptide addition. After 4 hrs at room temperature the reaction was stopped by addition of 10 µl of 10mM Cystein. An aliquot of the conjugate reaction mixture was diluted 1:100 with 0.1M sodium bicarbonate buffer and immediately filled into the wells (100 µl) of ELISA plates (Nunc Immuno-Plate). After standing 16 hrs at 4°C 100 µl blocking buffer (as above) was added to each well and incubated for another 30 minutes. The plates were washed with 2x300 µl/well TBST (as above) and filled with 100 µl antibody at 10 µg/ml or 2 µg/ml in blocking buffer. The plates were kept 16 hours at 4°C and washed with 2x300 µl TBST. 100 µl/well HRP-conjugated anti-human Ig H+L (Pierce, dilution 1:1000 with blocking buffer) was added and incubated for 1 hour at ambient temperature. The plates were washed with 3x300ul/well TBST. Colour development was started by addition of 100 µl tetra-methyl benzidine/hydrogen peroxide reagent. The reaction was stopped after 5 minutes by addition of 100 µl/well 1M sulfuric acid and the optical density is measured by an opticalreader (Microplate Reader 3550, BioRad) at 450 nm. For comparison mouse monoclonal

antibodies were analysed in the same way, except using as revealing agent HRP-labelled anti-mouse Ig instead of anti-human Ig.

Employing specific of the above described heptapeptides derived from A β , specific ELISA-tests as described herein above were carried out. Preferably, inventive antibodies comprise antibodies which show, as measured by of optical densities, a signal to background ratio above "10" when their reactivity with an A-beta derived peptide (AEFRHD; amino acid 2 to 7 of A-beta) is compared to an non-related protein/peptide like BSA. Most preferably, the ratio of optical densities is above "5" for a corresponding reaction with at least one of the following three A β derived peptides: (VFFAED; amino acid 18 to 23 of A β) or (FFAEDV; amino acid 19 to 24 of A β) or (LVFFAE; amino acid 17 to 22 of A β).

Corresponding results for the inventive parental and/or matured antibodies are shown in the following two tables:

MS-R #	Peptide2-7 2-7/BSA	Peptide 17-22 17-22/BSA	Peptide 18-23 18-23/BSA	Peptide 19-24 19-24/BSA	Peptide-ratio 17-22/2-7	Peptide-ratio 18-23/2-7	Peptide-ratio 19-24/2-7
7	24	4	7	4	0.17	0.29	0.17
8	28	10	29	25	0.36	1.04	0.89
7.2	34	12	16	9	0.35	0.47	0.26
7.3	34	11	15	9	0.32	0.44	0.26
7.4	36	10	13	6	0.28	0.36	0.17
7.9	28	9	13	8	0.32	0.46	0.29
7.11	37	11	15	9	0.30	0.41	0.24
7.12	38	6	8	7	0.16	0.21	0.18
8.1	30	1	11	8	0.03	0.37	0.27
8.2	32	4	28	23	0.13	0.88	0.72
3.2H2	26	12	23	20	0.46	0.88	0.77
3.3H1	23	4	12	8	0.17	0.52	0.35
3.3H3	31	2	5	2	0.06	0.16	0.06
3.4H1	27	2	8	2	0.07	0.30	0.07
3.4H2	16	11	1	1	0.69	0.06	0.06
3.4H3	22	9	17	11	0.41	0.77	0.50
3.4H5	28	5	13	4	0.18	0.46	0.14
3.4H7	24	2	6	5	0.08	0.25	0.21
3.4H17	28	5	12	11	0.18	0.43	0.39
3.4L11	31	6	20	5	0.19	0.65	0.16
3.6H6	25	1	4	7	0.04	0.16	0.28
3.6H1	23	3	13	5	0.13	0.57	0.22

3.6H2	19	2	8	3	0.11	0.42	0.16
7.2H1	38	8	11	9	0.21	0.29	0.24
7.2H2	16	10	10	10	0.63	0.63	0.63
7.2H3	33	17	20	18	0.52	0.61	0.55
7.2H4	23	12	13	12	0.52	0.57	0.52
7.2H5	30	13	18	15	0.43	0.60	0.50
7.2L1	24	14	16	11	0.57	0.68	0.45
7.4H1	31	16	20	16	0.52	0.65	0.51
7.4H2	36	17	20	16	0.47	0.56	0.46
7.9H1	32	7	12	6	0.23	0.36	0.19
7.9H2	35	3	6	8	0.08	0.16	0.23
7.9H3	35	11	20	9	0.31	0.57	0.27
7.9H4	30	10	15	7	0.32	0.49	0.22
7.11H1	31	8	9	8	0.25	0.29	0.25
7.11H2	34	10	12	14	0.29	0.36	0.41
7.12L1	16	10	12	10	0.60	0.70	0.59
8.1H1	29	22	25	25	0.77	0.88	0.86
8.2H1	22	7	23	20	0.34	1.05	0.94
8.2L1	26	15	32	31	0.60	1.26	1.22

Table 6: Reactivity of MS-R Fabs with BSA-conjugated Abeta heptapeptides 2-7 (AEFRHD), 17-22 (LVFFAE), 18-23 (VFFAED) and 19-24 (FFAEDV). The ratios of the ELISA read-out (optical density) obtained with peptide-conjugated and non-conjugated BSA are given. The signal intensities obtained with the 17-22, 18-23 and 19-24 peptides in relation to the 2-7 peptide are also indicated.

MS-R IgG	AEFRHD	LVFFAE	VFFAED	FFAEDV	Peptide-ratio	Peptide-ratio	Peptide-ratio
#	2-7/BSA	17-22/BSA	18-23/BSA	19-24/BSA	17-22/2-7	18-23/2-7	19-24/2-7
3.3	17	11	16	11	0.65	0.94	0.65
7.12	19	11	13	11	0.58	0.68	0.58
8.1	16	7	16	14	0.44	1.00	0.88
3.4H7	22	3	16	15	0.14	0.73	0.68
7.9H2	13	5	8	6	0.38	0.62	0.46
7.9H3	13	6	8	6	0.46	0.62	0.46
7.9.H7	30	5	16	10	0.17	0.53	0.33
7.11H2	10	6	7	6	0.60	0.70	0.60
8.2.H2	18	10	15	14	0.56	0.83	0.78
3.6.H5x3.6.L2	11	7	9	8	0.64	0.82	0.73
7.11.H2x7.9.L 1 (L1)	14	8	10	9	0.57	0.71	0.64
8.2.H2x8.2.L1	13	20	25	25	1.54	1.92	1.92
<i>Mouse mab</i>							
BAP-1	21	1	1	1	0.05	0.05	0.05
BAP-2	21	1	1	1	0.05	0.05	0.05
4G8	1	23	20	1	23	20	1
6E10	18	1	1	1	0.06	0.06	0.06
6F/3D*	1	1	1	1	1	1	1
Amy 33	16	2	1	3	0.13	0.06	0.19

Table 7: Reactivity of MS-R IgGs and mouse monoclonal antibodies BAP-1, BAP-2, 4G8, 6E10 Amy-33 and 6F/3D with BSA-conjugated A β heptapeptides 2-7 (AEFRHD), 17-22 (LVFFAE), 18-23 (VFFAED) and 19-24 (FFAEDV). The ratios of the ELISA read-out (optical density) obtained with peptide-conjugated and non-conjugated BSA are given. The signal intensities obtained with the 17-22, 18-23 and 19-24 peptides in relation to the 2-7 peptide are also indicated. * this antibody is specific for sequence 8-17 and does not recognize N-terminal or middle epitope sequences.

EXAMPLE 13: Combination of optimized H-CDR2 and L-CDR1 by cross-cloning

The modular design of the HuCAL library allows exchange of complementarity determining regions (CDRs) of two different Fab encoding genes in a simple cloning

step. For a further improvement of affinity the independently optimized H-CDR2 and L-CDR1 from matured clones with the same H-CDR3 were combined, because there was a high probability that this combination would lead to a further gain of affinity (Yang et al., 1995, J.Mol.Biol. 254, 392-403; Schier et al., 1996b, J.Mol.Biol. 263, 551-567; Chen et al., 1999, J.Mol.Biol. 293, 865-881). Whole light chains, or fragments thereof, were transferred from an L-CDR1 optimized donor clone to a H-CDR2 optimized recipient clone. Donor and recipient clones were only combined, if both carried identical H-CDR3 sequences. All donor and recipient clones carried the VH3-V κ 3 framework.

This was accomplished by transferring whole light chains from the L-CDR1-optimized donor clone to the H-CDR2-optimized recipient clone. Epitope specificity was conserved by only combining clones with the same H-CDR3. By light chain exchange a H-CDR2-optimized clone obtained only an optimized L-CDR1, if the exchange occurred between clones with the same L-CDR3. If the L-CDR3 of the clones to be combined was different, the H-CDR2-optimized clone acquired in addition to the optimized L-CDR1 another L-CDR3 (L-CDR2 remained the HuCAL consensus sequence (Knappik et al., 2000)) and when derivatives of MS-Roche #7.12 were used as donors of the light chain L-CDR1, 2 and 3 were exchanged in the H-CDR2-optimized acceptor clone. Three different cloning strategies were employed:

- 1) Using restriction endonucleases XbaI and SphI the whole antibody light chain fragment was excised from plasmid 1 (e.g. pMx9_Fab_MS-Roche#7.11.H1_FS) and the thereby obtained vector backbone was then ligated to the light chain fragment of plasmid 2 (e.g. pMx9_Fab_MS-Roche#7.2.L1_FS) generated by XbaI and SphI digest. Thereby a new plasmid (nomenclature: pMx9_Fab_MS-Roche#7.11.H1x7.2.L1_FS) was created encoding L-CDR1,2,3 of parental clone #7.2.L1 and H-CDR1,2,3 of parental clone #7.11.H1.
- 2) Using restriction endonucleases XbaI and Acc65I an L-CDR1 coding fragment was excised from plasmid 1 (e.g. pMx9_Fab_MS-Roche#7.11.H2_FS) and the thereby obtained vector backbone was then ligated to the L-CDR1 fragment of plasmid 2 (e.g. pMx9_Fab_MS-Roche#7.12.L1_FS) generated by XbaI and Acc65I. Thereby a new plasmid (nomenclature: pMx9_Fab_MS-

Roche#7.11.H2x7.12.L1(L-CDR1)_FS) was created encoding L-CDR1 of parental clone #7.12.L1 while L-CDR2,3 and H-CDR1,2,3 are derived from parental clone #7.11.H2.

- 3) Using restriction endonucleases XbaI and BamHI an L-CDR1 and L-CDR2 coding fragment was excised from plasmid 1 (e.g. pMx9_Fab_MS-Roche#7.11.H2_FS) and the thereby obtained vector backbone was then ligated to the L-CDR1 and L-CDR2 fragment of plasmid 2 (e.g. pMx9_Fab_MS-Roche#7.12.L1_FS) generated by XbaI and BamHI digest. Thereby a new plasmid (nomenclature: pMx9_Fab_MS-Roche#7.11.H2x7.12.L1(L-CDR1+2)_FS) was created encoding L-CDR1 and L-CDR2 of parental clone #7.12.L1 while L-CDR3 and H-CDR1,2,3 are derived from parental clone #7.11.H2.

Illustrative examples for the different cloning strategies as well as for sequences donor and recipient clones are given in table 8.

After large scale expression and purification their affinities were determined on A β (1-40) fibers. Furthermore, K_D values for selected cross-cloned MS-R Fab/antibodies are given in appended Table 9.

Binder name	L-CDR1	pos.49	L-CDR2	pos. 85	L-CDR3	H-CDR1	pos.47	H-CDR2	H-CDR3
-------------	--------	--------	--------	---------	--------	--------	--------	--------	--------

↓
cloning strategy 1)



MS-Roche #7.11.H1	RASQSVSSSYLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	GINAAGFRTYYADSVKG	GKGNTHKPYGVRYFDV
MS-Roche #7.2.L1	RASQYVDRITYLA	Y	GASSRAT	T	QQIYSFPH	GFTFSSYAMS	W	AINSGSGSTYYADSVKG	GKGNTHKPYGVRYFDV
MS-Roche #7.11.H1x7.2.L1	RASQYVDRITYLA	Y	GASSRAT	T	QQIYSFPH	GFTFSSYAMS	W	GINAAGFRTYYADSVKG	GKGNTHKPYGVRYFDV

↓
cloning strategy 2)



MS-Roche #7.11.H2	RASQSVSSSYLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	AINANGYKKYYADSVKG	GKGNTHKPYGVRYFDV
MS-Roche #7.12.L1	RASQYVFRYYLA	S	GSSNRAT	V	LQLYNIPN	GFTFSSYGMS	W	NISGSGSTYYADSVKG	GKGNTHKPYGVRYFDV
MS-Roche #7.11.H2x7.12.L1(LCDR1)	RASQYVFRYYLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	AINANGYKKYYADSVKG	GKGNTHKPYGVRYFDV

↓
cloning strategy 3)



MS-Roche #7.11.H2	RASQSVSSSYLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	AINANGYKKYYADSVKG	GKGNTHKPYGVRYFDV
MS-Roche #7.12.L1	RASQYVFRYYLA	S	GSSNRAT	V	LQLYNIPN	GFTFSSYGMS	W	NISGSGSTYYADSVKG	GKGNTHKPYGVRYFDV

MS-Roche #7.11.H2x7.12.L1(LCDR1+2)	RASQVVFRRYLA	S	GSSNRAT	T	QQVYSPPH	GFTSSYAMS	W	AINANGYKYYADSVKG	GKGNTHKPYGYVRYFDV
Binder name	L-CDR1	pos.49	L-CDR2	pos. 85	L-CDR3	H-CDR1	pos.47	H-CDR2	H-CDR3
MS-Roche #3.6H5	RASQSVSSSYLA	Y	GASSRAT	V	QQTYNYPP	GFTSSYAMS	W	AISESGTKYYADSVKG	LTHYARYRYFDV
MS-Roche #3.6L2	RASQFLSRYLA	Y	GASSRAT	V	QQTYNYPP	GFTSSYAMS	W	AISGSGSTYYADSVKG	LTHYARYRYFDV
MS-Roche #3.6H5x3.6L2	RASQFLSRYLA	Y	GASSRAT	V	QQTYNYPP	GFTSSYAMS	W	AISESGTKYYADSVKG	LTHYARYRYFDV
MS-Roche #3.6H8	RASQSVSSSYLA	Y	GASSRAT	V	QQTYNYPP	GFTSSYAMS	W	AISEVSKFYADSVKG	LTHYARYRYFDV
MS-Roche #3.6L2	RASQFLSRYLA	Y	GASSRAT	V	QQTYNYPP	GFTSSYAMS	W	AISGSGSTYYADSVKG	LTHYARYRYFDV
MS-Roche #3.6H8x3.6L2	RASQFLSRYLA	Y	GASSRAT	V	QQTYNYPP	GFTSSYAMS	W	AISEVSKFYADSVKG	LTHYARYRYFDV
MS-Roche #7.4.H2	RASQSVSSSYLA	Y	GASSRAT	V	QQIYNFPH	GFTSSYAMS	W	AINYNGARIYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.2.L1	RASQYVDRTYLA	Y	GASSRAT	T	QQIYSFPH	GFTSSYAMS	W	AISGSGSTYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.4.H2x7.2.L1	RASQYVDRTYLA	Y	GASSRAT	T	QQIYSFPH	GFTSSYAMS	W	AINYNGARIYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.9H2	RASQSVSSSYLA	Y	GASSRAT	T	LQIYNMPI	GFTSSYAMS	W	AINADGNRKYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.12L2	RASQRFFYKYLA	S	GSSNRAT	V	LQLYNIPN	GFTSSYGMS	W	NISGSGSTYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.9H2x7.12L2	RASQRFFYKYLA	S	GSSNRAT	V	LQLYNIPN	GFTSSYAMS	W	AINADGNRKYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.9H4	RASQSVSSSYLA	Y	GASSRAT	T	LQIYNMPI	GFTSSYAMS	W	AINAVGMKKFYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.12.L2	RASQRFFYKYLA	S	GSSNRAT	V	LQLYNIPN	GFTSSYGMS	W	NISGSGSTYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.9H4x7.12L2	RASQRFFYKYLA	S	GSSNRAT	V	LQLYNIPN	GFTSSYAMS	W	AINAVGMKKFYADSVKG	GKGNTHKPYGYVRYFDV

MS-Roche #7.11H1	RASQSVSSSYLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	GINAAGFRITYADSVKKG	GKGNTHKPYGVRVYFDV
MS-Roche #7.11L1	RASQRILRIYLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	AISGSGGSTYYADSVKKG	GKGNTHKPYGVRVYFDV
Binder name	L-CDR1	pos.49	L-CDR2	pos. 85	L-CDR3	H-CDR1	pos.47	H-CDR2	H-CDR3
MS-Roche #7.11H1x7.11L1	RASQRILRIYLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	GINAAGFRITYADSVKKG	GKGNTHKPYGVRVYFDV
MS-Roche #7.11H1	RASQSVSSSYLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	GINAAGFRITYADSVKKG	GKGNTHKPYGVRVYFDV
MS-Roche #7.2L1	RASQYVDRTYLA	Y	GASSRAT	T	QQIYSFPH	GFTFSSYAMS	W	AISGSGGSTYYADSVKKG	GKGNTHKPYGVRVYFDV
MS-Roche #7.11H1x7.2L1	RASQYVDRTYLA	Y	GASSRAT	T	QQIYSFPH	GFTFSSYAMS	W	GINAAGFRITYADSVKKG	GKGNTHKPYGVRVYFDV
MS-Roche #3.3H1	RASQSVSSSYLA	Y	GASSRAT	V	HQMSYPP	GFTFSSYAMS	W	VISEKSRFIYADSVKKG	LTHYARYRYFDV
MS-Roche #3.4L9	RASRRIHVYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISGSGGSTYYADSVKKG	LTHYARYRYFDV
MS-Roche #3.3H1x3.4L9	RASRRIHVYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	VISEKSRFIYADSVKKG	LTHYARYRYFDV
MS-Roche #3.4H1	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISETSIKRYADSVKKG	LTHYARYRYFDV
MS-Roche #3.4L9	RASRRIHVYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISGSGGSTYYADSVKKG	LTHYARYRYFDV
MS-Roche #3.4H1x3.4L9	RASRRIHVYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISETSIKRYADSVKKG	LTHYARYRYFDV
MS-Roche #3.4H3	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	VISOTGRKIYADSVKKG	LTHYARYRYFDV
MS-Roche #3.4L7	RASQRLGRLYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISGSGGSTYYADSVKKG	LTHYARYRYFDV
MS-Roche #3.4H3x3.4L7	RASQRLGRLYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	VISOTGRKIYADSVKKG	LTHYARYRYFDV
MS-Roche #3.4H3	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	VISOTGRKIYADSVKKG	LTHYARYRYFDV
MS-Roche #3.4L9	RASRRIHVYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISGSGGSTYYADSVKKG	LTHYARYRYFDV
MS-Roche #3.4H3x3.4L9	RASRRIHVYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	VISOTGRKIYADSVKKG	LTHYARYRYFDV
MS-Roche #3.4H7	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	VISETGKNIYADSVKKG	LTHYARYRYFDV
MS-Roche #3.4L9	RASRRIHVYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISGSGGSTYYADSVKKG	LTHYARYRYFDV
MS-Roche #3.4H7x3.4L9	RASRRIHVYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	VISETGKNIYADSVKKG	LTHYARYRYFDV

MS-Roche #3.4H7	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GTFSSYAMS	W	VSETGKNIYADSVKG	LTHYARYRYFDV
MS-Roche #3.4L7	RASQRLGRLYLA	Y	GASSRAT	T	QQTYDYPP	GTFSSYAMS	W	AISGGSTYYADSVKG	LTHYARYRYFDV
Binder name	L-CDR1	pos.49	L-CDR2	pos. 85	L-CDR3	H-CDR1	pos.47	H-CDR2	H-CDR3
MS-Roche #3.4H7x3.4L7	RASQRLGRLYLA	Y	GASSRAT	T	QQTYDYPP	GTFSSYAMS	W	VSETGKNIYADSVKG	LTHYARYRYFDV
MS-Roche #3.6H5	RASQSVSSSYLA	Y	GASSRAT	V	QQTYNYPP	GTFSSYAMS	W	AISESGTKIYADSVKG	LTHYARYRYFDV
MS-Roche #3.6L1	RASQFIQRFYLA	Y	GASSRAT	V	QQTYNYPP	GTFSSYAMS	W	AISGGSTYYADSVKG	LTHYARYRYFDV
MS-Roche #3.6H5x3.6L1	RASQFIQRFYLA	Y	GASSRAT	V	QQTYNYPP	GTFSSYAMS	W	AISESGTKIYADSVKG	LTHYARYRYFDV
MS-Roche #7.2H2	RASQSVSSSYLA	Y	GASSRAT	T	QQIYSFPH	GTFSSYAMS	W	AINGTGMKYYADSVKG	GKGNTHKPYGVVRYFDV
MS-Roche #7.2L1	RASQYVDRITYLA	Y	GASSRAT	T	QQIYSFPH	GTFSSYAMS	W	AISGGSTYYADSVKG	GKGNTHKPYGVVRYFDV
MS-Roche #7.2H2x7.2L1	RASQYVDRITYLA	Y	GASSRAT	T	QQIYSFPH	GTFSSYAMS	W	AINGTGMKYYADSVKG	GKGNTHKPYGVVRYFDV
MS-Roche #7.4H2	RASQSVSSSYLA	Y	GASSRAT	V	QQIYNFPH	GTFSSYAMS	W	AINYNGARIYADSVKG	GKGNTHKPYGVVRYFDV
MS-Roche #7.12L2	RASQRFYKYLA	S	GSSNRAT	V	LQLYNIPN	GTFSSYGMS	W	NISGSGSTYYADSVKG	GKGNTHKPYGVVRYFDV
MS-Roche #7.4H2x7.12L2	RASQRFYKYLA	S	GSSNRAT	V	LQLYNIPN	GTFSSYAMS	W	AINYNGARIYADSVKG	GKGNTHKPYGVVRYFDV
MS-Roche #7.9H2	RASQSVSSSYLA	Y	GASSRAT	T	LQIYNMPI	GTFSSYAMS	W	AINADGNRKYADSVKG	GKGNTHKPYGVVRYFDV
MS-Roche #7.2L1	RASQYVDRITYLA	Y	GASSRAT	T	QQIYSFPH	GTFSSYAMS	W	AISGGSTYYADSVKG	GKGNTHKPYGVVRYFDV
MS-Roche #7.9H2x7.2L1	RASQYVDRITYLA	Y	GASSRAT	T	QQIYSFPH	GTFSSYAMS	W	AINADGNRKYADSVKG	GKGNTHKPYGVVRYFDV
MS-Roche #7.11H2	RASQSVSSSYLA	Y	GASSRAT	T	QQVVSPPH	GTFSSYAMS	W	AINANGYKYYADSVKG	GKGNTHKPYGVVRYFDV
MS-Roche #7.2L1	RASQYVDRITYLA	Y	GASSRAT	T	QQIYSFPH	GTFSSYAMS	W	AISGGSTYYADSVKG	GKGNTHKPYGVVRYFDV
MS-Roche #7.11H2x7.2L1	RASQYVDRITYLA	Y	GASSRAT	T	QQIYSFPH	GTFSSYAMS	W	AINANGYKYYADSVKG	GKGNTHKPYGVVRYFDV
MS-Roche #7.9H2	RASQSVSSSYLA	Y	GASSRAT	T	LQIYNMPI	GTFSSYAMS	W	AINADGNRKYADSVKG	GKGNTHKPYGVVRYFDV

MS-Roche #7.12L1	RASQYVFRRYLA	S	GSSNRAT	V	LQLYNIPN	GFTFSSYGMS	W	NISGSGSSTYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.9H2x7.12L1	RASQYVFRRYLA	S	GSSNRAT	V	LQLYNIPN	GFTFSSYAMS	W	AINADGNRKYYADSVKG	GKGNTHKPYGYVRYFDV
Binder name	L-CDR1	pos.49	L-CDR2	pos. 85	L-CDR3	H-CDR1	pos.47	H-CDR2	H-CDR3
MS-Roche #7.11H2	RASQSVSSSYLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	AINANGYKKYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.9L1	RASQRLSPRYLA	Y	GASSRAT	T	LQIYNMPI	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.11H2x7.9L1	RASQRLSPRYLA	Y	GASSRAT	T	LQIYNMPI	GFTFSSYAMS	W	AINANGYKKYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #8.1H1	RASQSVSSSYLA	Y	GASSRAT	T	QQLSNYPP	GFTFSSYAMS	W	AISRSGSNIYYADSVKG	LLSRGYNNGYYHKFDV
MS-Roche #8.2L1	RASQRVSGRYLA	Y	GASSRAT	T	QQLSNYPP	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	LLSRGYNNGYYHKFDV
MS-Roche #8.1H1x8.2L1	RASQRVSGRYLA	Y	GASSRAT	T	QQLSNYPP	GFTFSSYAMS	W	AISRSGSNIYYADSVKG	LLSRGYNNGYYHKFDV
MS-Roche #7.11H2	RASQSVSSSYLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	AINANGYKKYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.12L1	RASQYVFRRYLA	S	GSSNRAT	V	LQLYNIPN	GFTFSSYGMS	W	NISGSGSSTYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.11H2x7.12L1	RASQYVFRRYLA	S	GSSNRAT	V	LQLYNIPN	GFTFSSYAMS	W	AINANGYKKYYADSVKG	GKGNTHKPYGYVRYFDV

Table 8 Arrows indicate the location of restriction enzyme sites used to digest corresponding plasmids

MS-R #	K_D A β ₁₋₄₀ nM	K_D A β ₁₋₄₂ nM
3.3H1x3.4L9	2.16	2.97
3.4H1x3.4L9	0.25	0.5
3.4H3x3.4L7	0.92	0.92
3.4H3x3.4L9	1.05	0.93
3.4H7x3.4L9	2.66	3.51
3.4H7x3.4L7	1.19	1.23
3.6H5x3.6L1	1.25	1.04
3.6H5x3.6L2	1.26	0.84
7.2H2x7.2L1	1.29	1.43
7.4H2x7.2L1	1.4	1.4
7.4H2x7.12L2	1.4	1.8
7.9H2x7.2L1(L1)	1.4	1.4
7.9H2x7.12L1	1.2	1.1
7.9H2x7.12L2(L1+2)	0.4	0.4
7.11H1x7.2L1	1.75	1.39
7.11H1x7.11L1	0.41	0.47
7.11H2x7.2L1(L1)	1	0.6
7.11H2x7.9L1 (L1)	0.1	1
8.1H1x8.2L1	1.3	1.6

Table 9: K_D values for crosscloned MS-R Fab binding to A β ₁₋₄₀ and A β ₁₋₄₂ fibers as determined in the Biacore. The preparation of crosscloned Fabs is described in example 13. The K_D values were determined by kinetic curve fittings and corrected for the content of active Fab present in each sample as described in the text. Some of the Fabs were additionally purified by size exclusion chromatography or preparative ultracentrifugation to remove aggregated material. (L1), the H-CDR2-matured acceptor clone received only L-CDR1 from the L-CDR1 improved donor clone; (L1+2), the H-CDR2-matured acceptor clone received L-CDR1+2 from the L-CDR1 improved donor clone.

Example 14: In vivo amyloid plaque decoration in a mouse model of Alzheimer's disease as revealed by confocal laser scanning microscopy and colocalization analysis.

Selected MS-R IgG1 antibodies were tested in APP/PS2 double transgenic mice (Reference: Richards et al., Soc. Neurosci. Abstr., Vol. 27, Program No. 5467, 2001) for amyloid plaque decoration in vivo. The antibodies (1 mg/mouse) were administered i.v. and after 3 days the brains were perfused with saline and prepared for cryosection. In another study the mice were exposed to higher concentrations of the antibodies, i.e. 2 mg injected i.v. at day 0, 3, and 6, and sacrificed at day nine. The presence of the antibodies bound to amyloid plaques was assessed on unfixed cryostat sections by double-labeled indirect immunofluorescence using goat anti-human IgG (H+L) conjugated to either Cy3 (#109-165-003, Jackson Immuno Research) followed by BAP-2-Alexa488 immunoconjugate. Imaging was done by confocal laser microscopy and image processing for quantitative detection of colocalizations by IMARIS and COLOCALIZATION software (Bitplane, Switzerland). Typical examples are shown in Figures 10-14. All of the MS-R antibodies tested were found positive in immunodecoration of amyloid plaques in vivo, although some variability was noted.

Example 15: Investigation of binding of different monoclonal antibodies to amyloid precursor protein (APP) on the surface of HEK293 cells:

APP is widely expressed in the central nervous system. Binding of antibody to cell surface APP may lead to complement activation and cell destruction in healthy brain areas. Therefore, it is mandatory for therapeutic A-beta antibodies to be devoid of reactivity towards APP. High affinity antibodies against the N-terminal domain of A-beta (e.g. BAP-1, BAP-2) recognize the respective epitope also in the framework of APP. In contrast, the antibodies against the middle epitope (e.g. 4G8), and the antibodies of the invention are surprisingly unable to recognize to cell surface APP. Thus, antibodies of the invention which decorate A-beta, but not APP in vivo, are superior to non-selective antibodies.

The method of flow cytometry is well known in the art. Relative units of fluorescence (FL1-H) measured by flow cytometry indicate cell surface binding of the respective antibody. A fluorescence shift on APP transfected HEK293 compared to untransfected HEK293 cells indicates the unwanted reaction with cell surface APP. As an example, antibodies BAP-1 and BAP-2 against the N-terminal domain show a significant shift of FL-1 signal in HEK293/APP (thick line) compared to untransfected HEK293 cells (dotted line). The 4G8 antibody (specific for the middle A-beta epitope) and all antibodies of the invention (specific for N-terminal and middle A-beta epitopes) show no significant shift in fluorescence. Differences in basal fluorescence between HE293/APP ad HEK293 cells are due to different cell size. A FACScan instrument was used in combination with the Cellquest Pro Software package (both Becton Dickinson).

Example 16: List of identified SEQ ID NOs relating to inventive antibody molecules

The appended table 10 relates to sequences as defined herein for some specific inventive antibody molecules.

Table 10: Identification of SEQ ID NOs for parental antibodies as well as optimized, matured and/or cross-cloned antibody molecules

Molecule #	VH prot	VL prot	VH DNA	VL DNA	HCDR3 prot	HCDR3 DNA	LCDR3 prot	LCDR3 DNA
3	4	10	3	9	22	21	16	15
7	6	12	5	11	24	23	18	17
8	8	14	7	13	26	25	20	19
3.6H5 x 3.6L2	33	47	32	46	61	60	75	74
3.6H8 x 3.6L2	35	49	34	48	63	62	77	76
7.4H2 x 7.2L1	37	51	36	50	65	64	79	78
7.9H2 x 7.12L2	39	53	38	52	67	66	81	80
7.9H4 x 7.12L2	41	55	40	54	69	68	83	82
7.11H1x7.11L1	43	57	42	56	71	70	85	84
7.11H1x7.2L1	45	59	44	58	73	72	87	86
7.9H7	89	91	88	90	93	92	95	94
3.3H1x3.4L9	295	325	294	324	355	354	385	384
3.4H1x3.4L9	297	327	296	326	357	356	387	386
3.4H3x3.4L7	299	329	298	328	359	358	389	388
3.4H3x3.4L9	301	331	300	330	361	360	391	390
3.4H7x3.4L9	303	333	302	332	363	362	393	392
3.4H7x3.4L7	305	335	304	334	365	364	395	394
3.6H5x3.6L1	307	337	306	336	367	366	397	396
7.2H2x7.2L1	309	339	308	338	369	368	399	398
7.4H2x7.12L2	311	341	310	340	371	370	401	400
7.9H2x7.2L1	313	343	312	342	373	372	403	402
7.9H2x7.12L1	315	345	314	344	375	374	405	404
7.11H2x7.2L1	317	347	316	346	377	376	407	406
7.11H2x7.9L1	319	349	318	348	379	378	409	408
7.11H2x7.12L1	321	351	320	350	381	380	411	410
8.1H1x8.2L1	323	353	322	352	383	382	413	412

Claims

1. An antibody molecule capable of specifically recognizing two regions of the β -A4 peptide/A β 4, wherein the first region comprises the amino acid sequence AEFRHDSGY as shown in SEQ ID NO: 1 or a fragment thereof and wherein the second region comprises the amino acid sequence VHHQKLVFFAEDVG as shown in SEQ ID NO: 2 or a fragment thereof.
2. The antibody molecule of claim 1, wherein said antibody molecule recognizes at least two consecutive amino acids within the two regions of β -A4.
3. The antibody molecule of claim 1 or 2, wherein said antibody molecule recognizes in the first region an amino acid sequence comprising: AEFRHD, EF, EFR, FR, EFRHDSG, EFRHD or HDSG and in the second region an amino acid sequence comprising: HHQKL, LV, LVFFAE, VFFAED or VFFA, FFAEDV.
4. The antibody molecule of any one of claims 1 to 3, wherein said antibody molecule comprises a variable V_H -region as encoded by a nucleic acid molecule as shown in a SEQ ID NO selected from the group consisting of SEQ ID NO: 3, 5 or 7 or a variable V_H -region as shown in a SEQ ID NO: selected from the group consisting of SEQ ID NOs: 4, 6 and 8.
5. The antibody molecule of any one of claims 1 to 3, wherein said antibody molecule comprises a variable V_L -region as encoded by a nucleic acid molecule as shown in a SEQ ID NO selected from the group consisting of SEQ ID NO: 9, 11 and 13 or a variable V_L -region as shown in a SEQ ID NO selected from the group consisting of SEQ ID NOs: 10, 12 and 14.

6. The antibody molecule of any one of claims 1 to 5, wherein said antibody molecule comprises at least one CDR3 of an V_L -region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 15, 17 or 19 or at least one CDR3 amino acid sequence of an V_L -region as shown in SEQ ID NOs: 16, 18 or 20 and/or wherein said antibody molecule comprises at least one CDR3 of an V_H -region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 21, 23 or 25 or at least one CDR3 amino acid sequence of an V_H -region as shown in SEQ ID NOs: 22, 24 or 26.
7. The antibody molecule of any one of claims 1 to 6, wherein said antibody is selected from the group consisting of MSR-3, -7 and -8 or an affinity-matured version of MSR-3, -7 or -8.
8. The antibody molecule of any one of claims 1 to 7, wherein said antibody molecule is a full antibody (immunoglobulin), a F(ab)-fragment, a F(ab)₂-fragment, a single-chain antibody, a chimeric antibody, a CDR-grafted antibody, a bivalent antibody-construct, a synthetic antibody or a cross-cloned antibody.
9. The antibody molecule of any one of claims 1 to 8, wherein said at least two regions of β -A4 form a conformational epitope or a discontinuous epitope.
10. The antibody molecule of claim 8 or 9, wherein said cross-cloned antibody is selected from the group consisting of
MS-R #3.3H1x3.4L9;
MS-R #3.6H5 x 3.6L2;
MS-R #3.6H8 x 3.6L2;
MS-R #7.4H2 x 7.2L1;
MS-R #7.9H2 x 7.12L2;
MS-R #7.9H4 x 7.12L2;
MS-R #7.11H1 x 7.11L1;
MS-R #7.11H1 x 7.2L1;
MS-R #3.4H1 x 3.4L9;

MS-R #3.4H3 x 3.4L7;
MS-R #3.4H3 x 3.4L9;
MS-R #3.4H7 x 3.4L9;
MS-R #3.4H7 x 3.4L7;
MS-R #3.6H5 x 3.6L1;
MS-R #7.2H2 x 7.2L1;
MS-R #7.4H2 x 7.12L2;
MS-R #7.9H2 x 7.2L1;
MS-R #7.9H2 x 7.12L1;
MS-R #7.11H2 x 7.2L1;
MS-R #7.11H2 x 7.9L1;
MS-R #7.11H2 x 7.12L1 or
MS-R #8.1H1 x 8.2L1.

11. A nucleic acid molecule encoding an antibody molecule of any one of claims 1 to 10.
12. A vector comprising the nucleic acid molecule of claim 11.
13. A host cell comprising the vector of claim 12.
14. A method for the preparation of an antibody molecule of any one of claims 1 to 10 comprising culturing the host cell of claim 13 under conditions that allow synthesis of said antibody molecule and recovering said antibody molecule from said culture.
15. A composition comprising an antibody molecule of any one of claims 1 to 10 or an antibody molecule produced by the method of claim 14.
16. The composition of claim 15, which is a pharmaceutical or a diagnostic composition.

17. Use of an antibody molecule of any one of claims 1 to 10 or an antibody molecule produced by the method of claim 14, of a nucleic acid molecule of claim 11, of a vector of claim 12 or a host of claim 13 for the preparation of a pharmaceutical composition for the prevention and/or treatment of a disease associated with amyloidogenesis and/or amyloid-plaque formation.
18. Use of an antibody molecule of any one of claims 1 to 10 or an antibody molecule produced by the method of claim 14 for the preparation of a diagnostic composition for the detection of a disease associated with amyloidogenesis and/or amyloid-plaque formation.
19. Use of an antibody molecule of any one of claims 1 to 10 or an antibody molecule produced by the method of claim 14 for the preparation of a pharmaceutical composition for the disintegration of β -amyloid plaques.
20. Use of an antibody molecule of any one of claims 1 to 10 or an antibody molecule produced by the method of claim 14 for the preparation of a pharmaceutical composition for passive immunization against β -amyloid plaque formation.
21. The use of claims 17 or 18, wherein said disease is dementia, Alzheimer's disease, motor neuropathy, Down's syndrome, Creutzfeldt Jacob disease, hereditary cerebral hemorrhage with amyloidosis Dutch type, Parkinson's disease, HIV-related dementia, ALS or neuronal disorders related to aging.
22. Kit comprising an antibody molecule of any one of claims 1 to 10, a nucleic acid molecule of claim 16, a vector of claim 17 or a host cell of claim 18.
23. A method for the optimization of an antibody molecule as defined in any one of claims 1 to 10 comprising the steps of
 - (a) constructing a library of diversified Fab antibody fragments derived from an antibody comprising at least one CDR3 of an V_H -region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 21, 23 or

- 25 or at least one CDR3 amino acid sequence of an V_H -region as shown in SEQ ID NOs: 22, 24 or 26;
- (b) testing the resulting Fab optimization library by panning against $A\beta/A\beta_4$;
 - (c) identifying optimized clones; and
 - (d) expressing of selected, optimized clones.
24. The method of claim 23 further comprising a step (ca), whereby the optimized clones are further optimized by cassette mutagenesis
25. The method of claim 23 or 24, wherein said $A\beta/A\beta_4$ in step (b) is aggregated $A\beta/A\beta_4$.
26. The method of any one of claims 23 to 25, wherein said identification in step (c) is carried out by koff-ranking.
27. A method for the preparation of a pharmaceutical composition comprising the steps of
- (a) optimization of an antibody according to the method of any one of claims 23 to 26; and
 - (b) formulating the optimized antibody/antibody molecule with an physiologically acceptable carrier.
28. A pharmaceutical composition prepared by the method of claim 27.

Sequence Summary of HuCAL-Fab1 Library

VL

Framework 1										Framework 2										CDR 2									
CDR 1										CDR 2										CDR 2									
Position	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
VLk1	D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q G I S - - - - S Y L A W Y Q Q K P G K A P K L L I Y A S S L Q S G V P																												
VLk2	D I V M T Q S P S S L S A S V G D R V T I T C R A S Q G I S - - - - S Y L A W Y Q Q K P G K A P K L L I Y L G S N R A S G V P																												
VLk3	D I V L T Q S P S S L S A S V G D R V T I T C R A S Q G I S - - - - S Y L A W Y Q Q K P G K A P K L L I Y L G S N R A S G V P																												
VLk4	D I V M T Q S P S S L S A S V G D R V T I T C R A S Q G I S - - - - S Y L A W Y Q Q K P G K A P K L L I Y L G S N R A S G V P																												
VLk1	D I V L T Q P P - S V S G A P G Q R V T I S C S G S S S N I G S - - - - N Y V S W Y Q Q L P G T A P K L L I Y D N N Q R P S G V P																												
VLk2	D I A L T Q P A - S V S G S P G Q S I T I S C T G T S S D V G G Y - - - - N Y V S W Y Q Q H P G K A P K L L I Y D V S N R P S G V S																												
VLk3	D I E L T Q P P - S V S V A P G Q T A R I S C S G D A L G D - - - - K Y A S W Y Q Q K P G K A P K L L I Y D D S D R P S G I P																												

1/43

VH

Fig. 1a

Framework 1										CDR 1										Framework 2										CDR 2																																		
1										2										3										4										5										6														
Position										Position										Position										Position										Position										Position														
1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0																									
M16I										BspEI										BspXI										XhoI																																		
Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S	G	G	T	F	S	S	-	-	Y	A	I	S	W	V	R	Q	A	P	G	Q	G	L	E	W	M	G	G	I	I	P	-	-	I	F	G	T	A	N	Y	A
Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S	V	K	V	S	C	K	A	S	G	Y	T	F	T	S	-	-	Y	Y	M	H	W	V	R	Q	A	P	G	Q	G	L	E	W	M	G	W	I	N	P	-	-	N	S	G	G	T	N	Y	A
Q	V	Q	L	K	E	S	G	P	A	L	V	K	P	T	Q	T	L	T	C	T	F	S	C	A	S	G	F	S	L	S	T	S	G	V	G	V	W	I	R	Q	P	P	G	K	A	L	E	W	L	A	L	I	D	-	-	W	D	D	D	K	Y	Y	S	
Q	V	Q	L	V	E	S	G	G	L	V	K	P	G	S	E	T	L	R	L	S	C	A	A	S	G	F	T	F	S	S	-	-	Y	A	M	S	W	V	R	Q	A	P	G	K	G	L	E	W	V	S	A	I	S	G	-	-	S	G	S	T	Y	Y	A	
Q	V	Q	L	V	E	S	G	P	L	V	K	P	S	E	T	L	S	L	T	C	T	V	S	G	G	S	I	S	S	-	-	Y	Y	W	S	W	V	R	Q	P	P	G	K	G	L	E	W	I	G	Y	I	-	-	Y	S	G	S	T	N	Y	N			
Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	E	S	L	K	I	S	C	K	G	S	G	S	F	T	S	-	-	Y	W	I	G	W	V	R	Q	M	P	G	K	L	E	W	M	G	I	I	Y	P	-	-	G	D	S	D	T	R	Y	S		
Q	V	Q	L	Q	S	G	P	G	L	V	K	P	S	Q	T	L	S	L	T	C	A	I	S	G	D	S	V	S	S	N	S	A	A	W	N	W	I	R	Q	S	P	G	R	L	E	W	L	G	R	T	Y	Y	R	-	-	S	K	W	Y	N	Y	A		

Fig. 1a

3/43

7A

VH

Framework 1																	CDR 1										Fr																			
1																	2										3										4									
MfeI																	BspEI																	BspXI												
1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	a	b	2	3	4	5	6	7	8	9	0	1	4													
CAG	GTG	CAA	TTG	GTT	CAG	TCT	GGC	GGG	GAA	GTG	AAA	AAA	CGG	GGC	AGC	AGC	GTG	AAA	GTG	AGC	TTC	AGC	AGC	-	-	TAT	GCG	ATT	AGC	TGG	GTG	CAC	CAA	GCC	CCT											
CAG	GTG	CAA	TTG	GTT	CAG	AGC	GGC	GGG	GAA	GTG	AAA	AAA	CGG	GGC	GGC	AGC	GTG	AAA	GTG	AGC	TTC	AGC	AGC	-	-	TAT	TAT	ATG	CAC	TGG	GTG	CAC	CAA	GCC	CCT											
CAG	GTG	CAA	TTG	AAA	GAA	AGC	GGC	CCG	GCC	CTG	GTG	AAA	CCG	ACC	CAA	ACC	CTG	ACC	CTG	ACC	TTC	AGC	CTG	TCC	AGC	TTC	GGC	GTG	GCG	TGG	ATT	CAC	CAG	CCG	CCT											
CAG	GTG	CAA	TTG	GTG	GAA	AGC	GGC	GGC	CTG	GTG	CAA	CGG	GGC	GGC	AGC	CTG	GCT	CTG	AGC	TGC	TCC	AGC	AGC	-	-	TAT	GCG	ATG	AGC	TGG	GTG	CAC	CAA	GCC	CCT											
CAG	GTG	CAA	TTG	GAA	AAT	GGT	GCG	GCC	CTG	GTG	AAA	CGG	AGC	GAA	ACC	CTG	AGC	CTG	AGC	CTG	ACC	GGT	TCC	AGC	AGC	ATT	AGC	AGC	-	-	TAT	TAT	TGG	AGC	TGG	ATT	CAC	CAG	CCG	CCT						
CAG	GTG	CAA	TTG	GTT	CAG	AGC	GGC	GGG	GAA	GTG	AAA	AAA	CGG	GGC	GAA	ACC	CTG	AAA	ATT	AGC	TGC	TCC	AGC	AGC	-	-	TAT	TGG	ATT	GCG	TGG	GTG	CAC	CAG	ATG	CCT										
CAG	GTG	CAA	TTG	CAA	CAG	TCT	GGT	CCG	GGC	CTG	GTG	AAA	CGG	AGC	CAA	ACC	CTG	AGC	CTG	ACC	TGT	GGC	ATT	TCC	GGC	GAT	AGC	GTG	AGC	AAC	AGC	GCG	GCG	TGG	AAC	TGG	ATT	CAC	CAG	TCT	CCT					

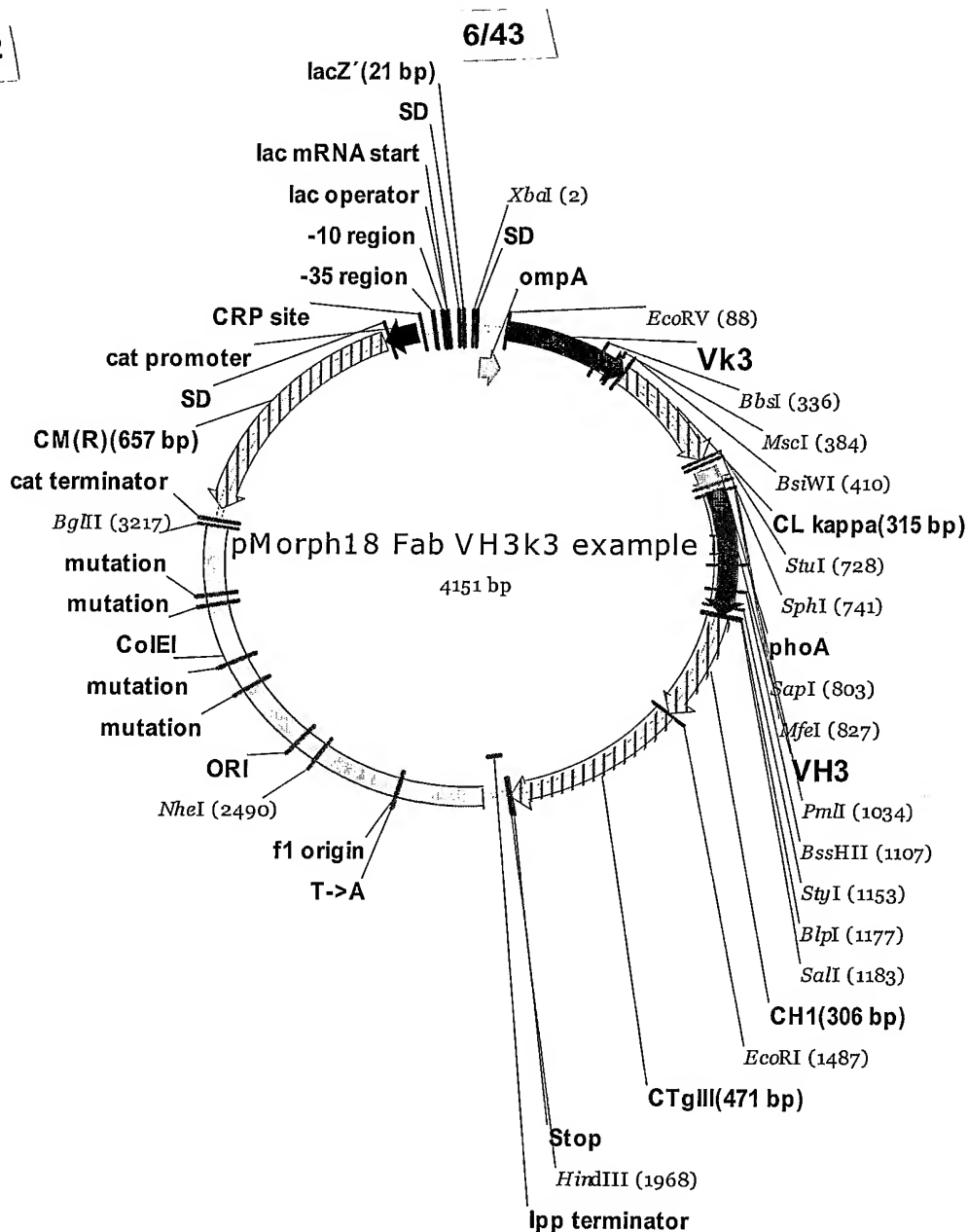
Fig. 1b cont.

Framework 2										Framework 3																		
CDR 2										CDR 2																		
5										6																		
4										7																		
8										8																		
CAG AAA	CCA GGT	AAA GCA	CCG AAA	CFA TTA	ATT TAT	GCA GCC	AGC AGC	TTG CAA	AGC TCC	GGG GTC	CCG TCC	CGT TTT	AGC GGC	TCT GGA	TCC GGC	ACT GGC	GAT TTT	ACC CTG	ACC ATT	TCC TCG	CTG CAA	GCT GAA	GAC TTT					
																								SexAI	AseI	SmaDI	BamHI	BstI
CAG AAA	CCA GGT	CAA AGC	CCG CAG	CFA TTA	ATT TAT	CTG GGC	AGC AAC	CGT GCC	AGT GGC	GTC CCG	GGG GTC	CCG TCC	CGT TTT	AGC GGC	TCT GGA	TCC GGC	ACT GGC	GAT TTT	ACC CTG	ACC ATT	TCC TCG	CTG CAA	GCT GAA	GAC TTT				
CAG AAA	CCA GGT	CAA GCA	CCG CGT	CFA TTA	ATT TAT	GGC GGC	AGC AGC	CGT GCA	ACT GGC	GTC CCG	GGG GTC	CCG TCC	CGT TTT	AGC GGC	TCT GGA	TCC GGC	ACT GGC	GAT TTT	ACC CTG	ACC ATT	TCC TCG	CTG CAA	GCT GAA	GAC TTT				
CAG AAA	CCA GGT	CAG CCG	CCG AAA	CFA TTA	ATT TAT	TGG GCA	TCC ACC	CGT GAA	AGC TCC	GTC CCG	GGG GTC	CCG TCC	CGT TTT	AGC GGC	TCT GGA	TCC GGC	ACT GGC	GAT TTT	ACC CTG	ACC ATT	TCC TCG	CTG CAA	GCT GAA	GAC TTT				
CAG TTG	CCC GGG	ACG CCG	CGG AAA	CTG CTG	ATT TAT	GAT AAC	AAC CAG	CGT CCG	TCA TCC	GTG CCG	GGG GTC	CCG TCC	CGT TTT	AGC GGC	TCT GGA	TCC GGC	ACT GGC	GAT TTT	ACC CTG	ACC ATT	TCC TCG	CTG CAA	GCT GAA	GAC TTT				
CAG CAT	CCC GGG	ACG CCG	CGG AAA	CTG CTG	ATT TAT	GAT GTG	AGC AAC	CGT CCG	TCA TCC	GTG CCG	GGG GTC	CCG TCC	CGT TTT	AGC GGC	TCT GGA	TCC GGC	ACT GGC	GAT TTT	ACC CTG	ACC ATT	TCC TCG	CTG CAA	GCT GAA	GAC TTT				
CAG AAA	CCC GGG	CAG CCG	CFA GTT	CTG CTG	ATT TAT	GAT GAT	TCT GAC	CGT CCG	TCA TCC	GTG CCG	GGG GTC	CCG TCC	CGT TTT	AGC GGC	TCT GGA	TCC GGC	ACT GGC	GAT TTT	ACC CTG	ACC ATT	TCC TCG	CTG CAA	GCT GAA	GAC TTT				
XhoI										BstI																		
CAG GGT	CTC GAG	TGG ATG	GGC TGG	ATG GGC	GGC ATT	ATT CCG	-	ATT TTT	GGC AGC	GGC AAC	TAC CCG	CAG AAG	TTT CAG	GGC CCG	GTG ACC	CGG GTG	ACC ATT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT			
GGG CAG	GGT CTC	GAG TGG	ATG GGC	TGG ATT	AAC CCG	-	-	AAT AGC	GGC GGC	AGC AAC	TAC CCG	CAG AAG	TTT CAG	GGC CCG	GTG ACC	CGG GTG	ACC ATT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT			
GGG AAA	GCC CTC	GAG TGG	CTG GCT	CTG ATT	GAT CCG	-	-	TGG GAT	GAT GAT	AGC TAT	TAT AGC	ACC AGC	CTG AAA	ACG CCG	TTT ACC	CGT TTT	ACC ATT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT			
GGG AAG	GGT CTC	GAG TGG	GTG AGC	GGC ATT	AGC GGT	-	-	AGC GGC	GGC AGC	ACC TAT	TAT CCG	GAT AGC	CTG AAA	GGC CCG	TTT ACC	CGT TTT	ACC ATT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT			
GGG AAG	GGT CTC	GAG TGG	ATT GGC	TAT ATT	TAT CCG	-	-	TAT AGC	GGC AAC	ACC AAC	TAT AAT	CCG AGC	CTG AAA	GGC CCG	TTT ACC	CGT TTT	ACC ATT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT			
GGG AAG	GGT CTC	GAG TGG	ATG GGC	ATT ATT	TAT CCG	-	-	GGC GAT	AGC GAT	ACC GAT	TAT TCT	CCG AGC	TTT CAG	GGC CCG	GTG ACC	CGG GTG	ACC ATT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT			
GGG CGT	GGC CTC	GAG TGG	CTG GGC	CGT ACC	TAT CCG	-	-	AGC AAA	TGG TAT	AAC GAT	TAT GCG	GTG AGC	GTG AAA	AGC CCG	TTT ACC	CGG GTG	ACC ATT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT			

Framework 2										Framework 3																		
CDR 2										CDR 2																		
5										6																		
4										7																		
8										8																		
CAG GGT	CTC GAG	TGG ATG	GGC TGG	ATG GGC	GGC ATT	ATT CCG	-	ATT TTT	GGC AGC	GGC AAC	TAC CCG	CAG AAG	TTT CAG	GGC CCG	GTG ACC	CGG GTG	ACC ATT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT			
																										XhoI	NspV	BstEII
CAG GGT	CTC GAG	TGG ATG	GGC TGG	ATG GGC	GGC ATT	AAC CCG	-	AAT AGC	GGC GGC	AGC AAC	TAC CCG	CAG AAG	TTT CAG	GGC CCG	GTG ACC	CGG GTG	ACC ATT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT			
GGG AAA	GCC CTC	GAG TGG	CTG GCT	CTG ATT	GAT CCG	-	-	TGG GAT	GAT GAT	AGC TAT	TAT AGC	ACC AGC	CTG AAA	ACG CCG	TTT ACC	CGT TTT	ACC ATT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT			
GGG AAG	GGT CTC	GAG TGG	GTG AGC	GGC ATT	AGC GGT	-	-	AGC GGC	GGC AGC	ACC TAT	TAT CCG	GAT AGC	CTG AAA	GGC CCG	TTT ACC	CGT TTT	ACC ATT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT			
GGG AAG	GGT CTC	GAG TGG	ATT GGC	TAT ATT	TAT CCG	-	-	TAT AGC	GGC AAC	ACC AAC	TAT AAT	CCG AGC	CTG AAA	GGC CCG	TTT ACC	CGG GTG	ACC ATT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT			
GGG AAG	GGT CTC	GAG TGG	ATG GGC	ATT ATT	TAT CCG	-	-	GGC GAT	AGC GAT	ACC GAT	TAT TCT	CCG AGC	TTT CAG	GGC CCG	GTG ACC	CGG GTG	ACC ATT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT			
GGG CGT	GGC CTC	GAG TGG	CTG GGC	CGT ACC	TAT CCG	-	-	AGC AAA	TGG TAT	AAC GAT	TAT GCG	GTG AGC	GTG AAA	AGC CCG	TTT ACC	CGG GTG	ACC ATT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT	ACC GCG	GAT TTT			

[illegible]

Fig. 2



	lacZ'	SD	ompA	
	~~~	~~~~~	~~~~~	
	XbaI			
	~~~~~			
			M K K T A I A I A V .	
1	TCTAGATAAC	GAGGGCAAAA	AATGAAAAAG	ACAGCTATCG CGATTGCAGT
	AGATCTATTG	CTCCCGTTTT	TTACTTTTTC	TGTTCGATAGC GCTAACGTCA
				Vk3
				~~~~~
			ompA	
			~~~~~	
			EcoRV	
			~~~~~	
	. A L A G F A T V A Q A D I V L T Q .			
51	GGCACTGGCT	GGTTTCGCTA	CCGTAGCGCA	GGCCGATATC GTGCTGACCC

7/43

Fig. 2 cont.

```

CCGTGACCGA CCAAAGCGAT GGCATCGCGT CCGGCTATAG CACGACTGGG
Vk3
~~~~~
. S P A T L S L S P G E R A T L S
101 AGAGCCCGGC GACCCTGAGC CTGTCTCCGG GCGAACGTGC GACCCTGAGC
TCTCGGGCCG CTGGGACTCG GACAGAGGCC CGCTTGCACG CTGGGACTCG
Vk3
~~~~~
C R A S Q S V S S S Y L A W Y Q Q .
151 TGCAGAGCGA GCCAGAGCGT GAGCAGCAGC TATCTGGCGT GGTACCAGCA
ACGTCTCGCT CGGTCTCGCA CTCGTCTCGT ATAGACCGCA CCATGGTCTG
Vk3
~~~~~
. K P G Q A P R L L I Y G A S S R A .
201 GAAACCAGGT CAAGCACCGC GTCTATTAAT TTATGGCGCG AGCAGCCGTG
CTTTGGTCCA GTTCGTGGCG CAGATAATTA AATACCGCGC TCGTCGGCAC
Vk3
~~~~~
. T G V P A R F S G S G S G T D F
251 CAACTGGGGT CCCGGCGCGT TTTAGCGGCT CTGGATCCGG CACGGATTTT
GTTGACCCCA GGGCCGCGCA AAATCGCCGA GACCTAGGCC GTGCCTAAAA
Vk3
~~~~~
BbsI
~~~~~
T L T I S S L E P E D F A V Y Y C .
301 ACCCTGACCA TTAGCAGCCT GGAACCTGAA GACTTTGCGG TGTATTATTG
TGGGACTGGT AATCGTCGGA CCTTGGACTT CTGAAACGCC ACATAATAAC
Vk3
~~~~~
MscI
~~~~~
. Q Q H Y T T P P T F G Q G T K V E .
351 CCAGCAGCAT TATACCACCC CGCCGACCTT TGGCCAGGGT ACGAAAGTTG
GGTCGTCTGTA ATATGGTGGG GCGGCTGGAA ACCGGTCCCA TGCTTTCAAC
CL kappa
~~~~~
Vk3
~~~~~
BsiWI
~~~~~
. I K R T V A A P S V F I F P P S
401 AAATTAAACG TACGGTGGCT GCTCCGAGCG TGTTTATTTT TCCGCCGAGC
TTTAATTTGC ATGCCACCGA CGAGGCTCGC ACAAATAAAA AGGCGGCTCG
CL kappa
~~~~~
D E Q L K S G T A S V V C L L N N .
451 GATGAACAAC TGAAAAGCGG CACGGCGAGC GTGGTGTGCC TGCTGAACAA
CTACTTGTTG ACTTTTCGCC GTGCCGCTCG CACCACACGG ACGACTTGTT
CL kappa
~~~~~
. F Y P R E A K V Q W K V D N A L Q .
501 CTTTTATCCG CGTGAAGCGA AAGTTCAGTG GAAAGTAGAC AACGCGCTGC
GAAAATAGGC GCACTTCGCT TTCAAGTCAC CTTTCATCTG TTGCGCGACG
CL kappa
~~~~~
. S G N S Q E S V T E Q D S K D S
551 AAAGCGGCAA CAGCCAGGAA AGCGTGACCG AACAGGATAG CAAAGATAGC
TTTCGCCGTT GTCGGTCCTT TCGCACTGGC TTGTCCTATC GTTTCATATC
CL kappa
~~~~~

```

8/43

Fig. 2 cont.

```

 T Y S L S S T L T L S K A D Y E K .
601 ACCTATTCTC TGAGCAGCAC CCTGACCCTG AGCAAAGCGG ATTATGAAAA
 TGGATAAGAG ACTCGTCGTG GGACTGGGAC TCGTTTCGCC TAATACTTTT
 CL kappa
      ~~~~~
      . H K V Y A C E V T H Q G L S S P V .
651  ACATAAAGTG TATGCGTGCG AAGTGACCCA TCAAGGTCTG AGCAGCCCGG
      TGTATTTTCAC ATACGCACGC TTCACTGGGT AGTTCCAGAC TCGTCGGGCC
              CL kappa
      ~~~~~
 StuI SphI
                                ~~~~~
      . T K S F N R G E A
701  TGAATAAATC TTTTAATCGT GGCGAGGCCT GATAAGCATG CGTAGGAGAA
      ACTGATTTAG AAAATTAGCA CCGCTCCGGA CTATTCGTAC GCATCCTCTT
              phoA
      ~~~~~
 SapI
                                ~~~~~
      M K Q S T I A L A L L P L L F .
751  AATAAAATGA AACAAAGCAC TATTGCACTG GCACTCTTAC CGTTGCTCTT
      TTATTTTACT TTGTTTCGTG ATAACGTGAC CGTGAGAATG GCAACGAGAA
              VH3
      ~~~~~
 phoA
      ~~~~~
      SapI
      ~~~~~
 MfeI
                                ~~~~~
      . T P V T K A Q V Q L V E S G G G L .
801  CACCCCTGTT ACCAAAGCCG AAGTGCAATT GGTGGAAGC GGC GGCGGCC
      GTGGGGACAA TGGTTTCGGC TTCACGTTAA CCACCTTTCG CCGCCGCCGG
              VH3
      ~~~~~
 . V Q P G G S L R L S C A A S G F
851 TGGTGCAACC GGGCGGCAGC CTGCGTCTGA GCTGCGCGGC CTCCGGATTT
 ACCACGTTGG CCCGCCGTCG GACGCAGACT CGACGCGCCG GAGGCCTAA
 VH3
      ~~~~~
      T F S S Y A M S W V R Q A P G K G .
901  ACCTTTAGCA GCTATGCGAT GAGCTGGGTG CGCCAAGCCC CTGGGAAGGG
      TGGAAATCGT CGATACGCTA CTCGACCCAC GCGGTTCTGGG GACCCTTCCC
              VH3
      ~~~~~
 . L E W V S A I S G S G G S T Y Y A .
951 TCTCGAGTGG GTGAGCGCGA TTAGCGGTAG CGGCGGCAGC ACCTATTATG
 AGAGCTCACC CACTCGCGCT AATCGCCATC GCCGCCGTCG TGGATAATAC
 VH3
      ~~~~~
                                PmlI
                                ~~~~~
 . D S V K G R F T I S R D N S K N
1001 CGGATAGCGT GAAAGGCCGT TTTACCATTT CACGTGATAA TTCGAAAAAC
 GCCTATCGCA CTTTCCGGCA AAATGGTAAA GTGCACTATT AAGCTTTTGT
 VH3
      ~~~~~
      T L Y L Q M N S L R A E D T A V Y .
1051 ACCCTGTATC TGCAAATGAA CAGCCTGCGT GCGGAAGATA CGGCCGTGTA
      TGGGACATAG ACGTTTACTT GTCGGACGCA CGCCTTCTAT GCCGGCACAT
              VH3
      ~~~~~
 BssHII

```

9/43

Fig. 2 cont.

```

 . Y C A R W G G D G F Y A M D Y W G .
1101 TTATTGCGCG CGTTGGGGCG GCGATGGCTT TTATGCGATG GATTATTGGG
 AATAACGCGC GCAACCCCGC CGCTACCGAA AATACGCTAC CTAATAACCC
 CH1
          ~~~~~
          VH3
          ~~~~~
 Sali
                                ~~~~~
          StyI                      BlnI
          ~~~~~                      ~~~~~
 . Q G T L V T V S S A S T K G P S
1151 GCCAAGGCAC CCTGGTGACG GTTAGCTCAG CGTCGACCAA AGGTCCAAGC
 CGGTTCCGTG GGACCACTGC CAATCGAGTC GCAGCTGGTT TCCAGGTTCC
 CH1
          ~~~~~
          V F P L A P S S K S T S G G T A A .
1201  GTGTTTCCGC TGGCTCCGAG CAGCAAAAAGC ACCAGCGGCG GCACGGCTGC
      CACAAAGGCG ACCGAGGCTC GTCGTTTTTCG TGGTCGCCGC CGTGCCGACG
                                CH1
          ~~~~~
 . L G C L V K D Y F P E P V T V S W .
1251 CCTGGGCTGC CTGGTTAAAG ATTATTTCCC GGAACCAGTC ACCGTGAGCT
 GGACCCGACG GACCAATTTC TAATAAAGGG CCTTGGTCAG TGGCACTCGA
 CH1
          ~~~~~
          . N S G A L T S G V H T F P A V L
1301  GGAACAGCGG GGCGCTGACC AGCGGCGTGC ATACCTTTCC GGCGGTGCTG
      CCTTGTGCGC CCGCGACTGG TCGCCGCACG TATGGAAAGG CCGCCACGAC
                                CH1
          ~~~~~
 Q S S G L Y S L S S V V T V P S S .
1351 CAAAGCAGCG GCCTGTATAG CCTGAGCAGC GTTGTGACCG TGCCGAGCAG
 GTTTCGTGCG CGGACATATC GGACTCGTCG CAACACTGGC ACGGCTCGTC
 CH1
          ~~~~~
          . S L G T Q T Y I C N V N H K P S N .
1401  CAGCTTAGGC ACTCAGACCT ATATTTGCAA CGTGAACCAT AAACCGAGCA
      GTCGAATCCG TGAGTCTGGA TATAAACGTT GCACTTGGTA TTTGGCTCGT
                                CH1
          ~~~~~
 EcoRI
                                ~~~~~
          . T K V D K K V E P K S E F G G G
1451  ACACCAAAGT GGATAAAAAA GTGGAACCGA AAAGCGAATT CGGGGGAGGG
      TGTGGTTTCA CCTATTTTTT CACCTTGGCT TTTCGCTTAA GCCCCCTCCC
                                CTgIII
          ~~~~~
 S G S G D F D Y E K M A N A N K G .
1501 AGCGGGAGCG GTGATTTTGA TTATGAAAAG ATGGCAAACG CTAATAAGGG
 TCGCCCTCGC CACTAAACT AATACTTTTC TACCGTTTGC GATTATTCCC
 CTgIII
          ~~~~~
          . A M T E N A D E N A L Q S D A K G .
1551  GGCTATGACC GAAAATGCCG ATGAAAACGC GCTACAGTCT GACGCTAAAG
      CCGATACTGG CTTTTACGGC TACTTTTGCG CGATGTCAGA CTGCGATTTC
                                CTgIII
          ~~~~~
 . K L D S V A T D Y G A A I D G F
1601 GCAAACCTGA TTCTGTCGCT ACTGATTACG GTGCTGCTAT CGATGGTTTC

```

10/43

Fig. 2 cont.

```

CGTTTGAAGT AAGACAGCGA TGAATAATGC CACGACGATA GCTACCAAAG
CTgIII
~~~~~
  I G D V S G L A N G N G A T G D F .
1651 ATTGGTGAAG TTTCCGGCCT TGCTAATGGT AATGGTGCTA CTGGTGATTT
TAACCACTGC AAAGGCCGGA ACGATTACCA TTACCACGAT GACCACTAAA
CTgIII
~~~~~
 . A G S N S Q M A Q V G D G D N S P .
1701 TGCTGGCTCT AATTCCCAA TGGCTCAAGT CGGTGACGGT GATAATTCAC
ACGACCGAGA TTAAGGGTTT ACCGAGTTCA GCCACTGCCA CTATTAAGTG
CTgIII
~~~~~
  . L M N N F R Q Y L P S L P Q S V
1751 CTTTAATGAA TAATTTCCTT CAATATTTAC CTTCCCTCCC TCAATCGGTT
GAAATTACTT ATTAAAGGCA GTTATAAATG GAAGGGAGGG AGTTAGCCAA
CTgIII
~~~~~
 E C R P F V F G A G K P Y E F S I .
1801 GAATGTCGCC CTTTGTCTT TGGCGCTGGT AAACCATATG AATTTTCTAT
CTTACAGCGG GAAAACAGAA ACCGCGACCA TTTGGTATAC TTAAAAGATA
CTgIII
~~~~~
  . D C D K I N L F R G V F A F L L Y .
1851 TGATTGTGAC AAAATAAACT TATTCCTGGT TGTCTTTGCG TTTCTTTTAT
ACTAACACTG TTTTATTTGA ATAAGGCACC ACAGAAACGC AAAGAAAATA
CTgIII
~~~~~
 . V A T F M Y V F S T F A N I L R
1901 ATGTTGCCAC CTTTATGTAT GTATTTTCTA CGTTTGCTAA CATACTGCGT
TACAACGGTG GAAATACATA CATAAAAGAT GCAAACGATT GTATGACGCA
CTgIII
~~~~~
                                Stop                lpp terminator
                                ~~~~
 HindIII
                                ~~~~~~

  N K E S
1951 AATAAGGAGT CTTGATAAGC TTGACCTGTG AAGTGAAAAA TGGCGCAGAT
TTATTCCTCA GAACTATTCG AACTGGACAC TTCACCTTTT ACCGCGTCTA
lpp terminator
~~~~~
2001 TGTGCGACAT TTTTFTTGTG TGCCGTTTAA TGAAATTGTA AACGTTAATA
ACACGCTGTA AAAAAACAG ACGGCAAATT ACTTTAACAT TTGCAATTAT
~~~~~
                                f1 origin
2051 TTTTGTTAAA ATTCGCGTTA AATTTTGTG AAATCAGCTC ATTTTFTAAC
AAAACAATTT TAAGCGCAAT TTAAAAACAA TTTAGTCGAG TAAAAAATTG
~~~~~
 f1 origin
2101 CAATAGGCCG AAATCGGCAA AATCCCTTAT AAATCAAAAG AATAGACCGA
GTTATCCGGC TTTAGCCGTT TTAGGGAATA TTTAGTTTTC TTATCTGGCT
~~~~~
                                f1 origin
2151 GATAGGGTTG AGTGTGTGTC CAGTTTGGAA CAAGAGTCCA CTATTAAAGA
CTATCCCAAC TCACAACAAG GTCAAACCTT GTTCTCAGGT GATAATTTCT
~~~~~
 f1 origin
2201 ACGTGGACTC CAACGTCAAA GGGCGAAAAA CCGTCTATCA GGGCGATGGC
TGCACCTGAG GTTGCAGTTT CCCGCTTTTT GGCAGATAGT CCCGCTACCG
~~~~~

```

11/43

f1 origin

Fig. 2 cont.

T-&gt;A

2251 CCACTACGAG AACCATCACC CTAATCAAGT TTTTGGGGT CGAGGTGCCG  
GGTGATGCTC TTGGTAGTGG GATTAGTTCA AAAAACCCCA GCTCCACGGC  
~~~~~

f1 origin

2301 TAAAGCACTA AATCGGAACC CTAAAGGGAG CCCCCGATTT AGAGCTTGAC
ATTTTCGTGAT TTAGCCTTGG GATTTCCTC GGGGGCTAAA TCTCGAACTG
~~~~~

f1 origin

2351 GGGGAAAGCC GCGAACGTG GCGAGAAAGG AAGGGAAGAA AGCGAAAGGA  
CCCCTTTCGG CCGCTTGAC CGCTCTTCC TTCCCTTCTT TCGCTTTCCT  
~~~~~

f1 origin

2401 GCGGGCGCTA GGGCGCTGGC AAGTGTAGCG GTCACGCTGC GCGTAACCAC
CGCCCGCGAT CCCGCGACCG TTCACATCGC CAGTGCGACG CGCATTGGTG
~~~~~

f1 origin

NheI

2451 CACACCCGCC GCGCTTAATG CGCCGCTACA GGGCGCGTGC TAGCCATGTG  
GTGTGGGCGG CGCGAATTAC GCGGCGATGT CCCGCGCACG ATCGGTACAC  
~~~~~

f1 origin

ColEI

2501 AGCAAAAGGC CAGCAAAAGG CCAGGAACCG TAAAAAGGCC GCGTTGCTGG
TCGTTTTCCG GTCGTTTTCC GGTCCCTGGC ATTTTCCCG CGCAACGACC
~~~~~

ColEI

ORI

2551 CGTTTTTCCA TAGGCTCCGC CCCCTGACG AGCATCACAA AAATCGACGC  
GCAAAAAGGT ATCCGAGGCG GGGGACTGC TCGTAGTGT TTTAGCTGCG  
~~~~~

ColEI

2601 TCAAGTCAGA GGTGGCGAAA CCCGACAGGA CTATAAAGAT ACCAGGCGTT
AGTTCAGTCT CCACCGCTTT GGGCTGTCCT GATATTCTA TGGTCCGCAA
~~~~~

ColEI

2651 TCCCCCTGGA AGCTCCCTCG TGCGCTCTCC TGTTCGACC CTGCCGCTTA  
AGGGGGACCT TCGAGGGAGC ACGCGAGAGG ACAAGGCTGG GACGGCGAAT  
~~~~~

ColEI

mutation

2701 CCGGATACCT GTCCGCC'TTT CTCCCTTCGG GAAGCGTGGC GCTTTCAT
GGCCTATGGA CAGGCGGAAA GAGGGAAGCC CTTCCGACCG CGAAAGAGTA
~~~~~

ColEI

mutation

2751 AGCTCACGCT GTAGGTATCT CAGTTCGGTG TAGGTCGTTC GCTCCAAGCT  
TCGAGTGCGA CATCCATAGA GTCAAGCCAC ATCCAGCAAG CGAGGTTCTGA  
~~~~~

ColEI

mutation

2801 GGGCTGTGTG CACGAACCCC CCGTTCAGTC CGACCGCTGC GCCTTATCCG
CCCGACACAC GTGCTTGGGG GGCAAGTCAG GCTGGCGACG CGGAATAGGC
~~~~~

ColEI

12/43

Fig. 2 cont.

```

2851  GTAAC TATCG TCTTGAGTCC AACCCGGTAA GACACGACTT ATCGCCACTG
      CATTGATAGC AGAACTCAGG TTGGGCCATT CTGTGCTGAA TAGCGGTGAC
      ~~~~~~
 ColEI
2901 GCAGCAGCCA CTGGTAACAG GATTAGCAGA GCGAGGTATG TAGGCGGTGC
 CGTCGTCGGT GACCATTGTC CTAATCGTCT CGCTCCATAC ATCCGCCACG
      ~~~~~~
                        ColEI
                                          mutation
2951  TACAGAGTTC TTGAAGTGGT GGCCTAACTA CGGCTACACT AGAAGAACAG
      ATGTCTCAAG AACTTCACCA CCGGATTGAT GCCGATGTGA TCTTCTTGTC
      ~~~~~~
 ColEI
 mutation
3001 TATTTGGTAT CTGCGCTCTG CTGTAGCCAG TTACCTTCGG AAAAAGAGTT
 ATAAACCATA GACGCGAGAC GACATCGGTC AATGGAAGCC TTTTCTCTAA
      ~~~~~~
                        ColEI
3051  GGTAGCTCTT GATCCGGCAA ACAAACCACC GCTGGTAGCG GTGGTTTTTT
      CCATCGAGAA CTAGGCCGTT TGTTTGGTGG CGACCATCGC CACCAAAAAA
      ~~~~~~
 ColEI
3101 TGTTTGCAAG CAGCAGATTA CGCGCAGAAA AAAAGGATCT CAAGAAGATC
 ACAAACGTTT GTCGTCTAAT GCGCGTCTTT TTTTCCTAGA GTTCTTCTAG
      ~~~~~~
                        ColEI
3151  CTTTGATCTT TTCTACGGGG TCTGACGCTC AGTGGAACGA AACTCACGT
      GAAACTAGAA AAGATGCCCC AGACTGCGAG TCACCTTGCT TTTGAGTGCA
      ~~~~~~
 ColEI
 cat terminator
                                          ~~~~~~
                        BglII
                        ~~~~~~
3201 TAAGGGATTT TGGTCAGATC TAGCACCAGG CGTTTAAGGG CACCAATAAC
 ATTCCCTAAA ACCAGTCTAG ATCGTGGTCC GCAAATTCCC GTGGTTATTG
      ~~~~~~
                        ColEI
                        cat terminator
                        ~~~~~~
3251 TGCCTTAAAA AAATTACGCC CCGCCCTGCC ACTCATCGCA GTACTGTTGT
 ACGGAATTTT TTTAATGCGG GCGGGGACGG TGAGTAGCGT CATGACAACA
      ~~~~~~
                        CM (R)
3301  AATTCATTAA GCATTCTGCC GACATGGAAG CCATCACAAA CGGCATGATG
      TTAAGTAATT CGTAAGACGG CTGTACCTTC GGTAGTGTTT GCCGTACTAC
      ~~~~~~
 CM (R)
3351 AACCTGAATC GCCAGCGGCA TCAGCACCTT GTCGCCTTGC GTATAATATT
 TTGGACTTAG CGGTCGCCGT AGTCGTGGAA CAGCGGAACG CATATTATAA
      ~~~~~~
                        CM (R)
3401  TGCCCATAGT GAAAACGGGG GCGAAGAAGT TGTCCATATT GGCTACGTTT
      ACGGGTATCA CTTTGTGCCC CGCTTCTTCA ACAGGTATAA CCGATGCAAA
      ~~~~~~
 CM (R)
3451 AAATCAAAAC TGGTGAAACT CACCCAGGGA TTGGCTGAGA CGAAAAACAT
 TTTAGTTTTG ACCACTTTGA GTGGGTCCCT AACCGACTCT GCTTTTGTGA
      ~~~~~~

```



13/43

Fig. 2 cont.

```

CM (R)
3501  ATTCTCAATA AACCCCTTTAG GGAAATAGGC CAGGTTTTCA CCGTAACACG
      TAAGAGTTAT TTGGGAAATC CCTTTATCCG GTCCAAAAGT GGCATTGTGC
      ~~~~~

CM (R)
3551 CCACATCTTG CGAATATATG TGTAGAAACT GCCGGAAATC GTCGTGGTAT
 GGTGTAGAAC GCTTATATAC ACATCTTTGA CGGCCTTTAG CAGCACCATA
      ~~~~~

CM (R)
3601  TCACTCCAGA GCGATGAAAA CGTTTCAGTT TGCTCATGGA AAACGGTGTA
      AGTGAGGTCT CGCTACTTTT GCAAAGTCAA ACGAGTACCT TTTGCCACAT
      ~~~~~

CM (R)
3651 ACAAGGGTGA ACACTATCCC ATATCACCAG CTCACCGTCT TTCATTGCCA
 TGTTCCCACT TGTGATAGGG TATAGTGGTC GAGTGGCAGA AAGTAACGGT
      ~~~~~

CM (R)
3701  TACGGAACTC CGGGTGAGCA TTCATCAGGC GGGCAAGAAT GTGAATAAAG
      ATGCCTTGAG GCCCACTCGT AAGTAGTCCG CCCGTTCTTA CACTTATTC
      ~~~~~

CM (R)
3751 GCCGGATAAA ACTTGTGCTT ATTTTCTTTT ACGGTCTTTA AAAAGGCCGT
 CGGCCTATTT TGAACACGAA TAAAAAGAAA TGCCAGAAAT TTTTCCGGCA
      ~~~~~

CM (R)
3801  AATATCCAGC TGAACGGTCT GGTATAGGT ACATTGAGCA ACTGACTGAA
      TTATAGGTCG ACTTGCCAGA CCAATATCCA TGTAACTCGT TGACTGACTT
      ~~~~~

CM (R)
3851 ATGCCTCAAA ATGTTCTTTA CGATGCCATT GGGATATATC AACGGTGGTA
 TACGGAGTTT TACAAGAAAT GCTACGGTAA CCCTATATAG TTGCCACCAT
      ~~~~~

CM (R)
3901  TATCCAGTGA TTTTTTCTC CATTTTAGCT TCCTTAGCTC CTGAAAATCT
      ATAGGTCACT AAAAAAGAG GTAAAATCGA AGGAATCGAG GACTTTTAGA
      ~~~~~
 CM (R) SD
      ~~~~~

cat promoter
3951  CGATAACTCA AAAAATACGC CCGGTAGTGA TCTTATTTC AATTGGTGAA
      GCTATTGAGT TTTTATGCG GGCCATCACT AGAATAAAGT AATACCACTT
      ~~~~~
 cat promoter
 CRP site
      ~~~~~
4001  AGTTGGAACC TCACCCGACG TCTAATGTGA GTTAGCTCAC TCATTAGGCA
      TCAACCTTGG AGTGGGCTGC AGATTACACT CAATCGAGTG AGTAATCCGT
      ~~~~~
 cat promoter
 start
 lac mRNA
 ~
 lac operator
      ~~~~~

-35 region
      ~~~~~
4051 CCCAGGCTT TACACTTTAT GCTTCCGGCT CGTATGTTGT GTGGAATTGT
 GGGGTCCGAA ATGTGAAATA CGAAGGCCGA GCATACAACA CACCTTAACA
 lac operator SD lacZ'
      ~~~~~

4101  GAGCGGATAA CAATTCACA CAGGAAACAG CTATGACCAT GATTACGAAT

```

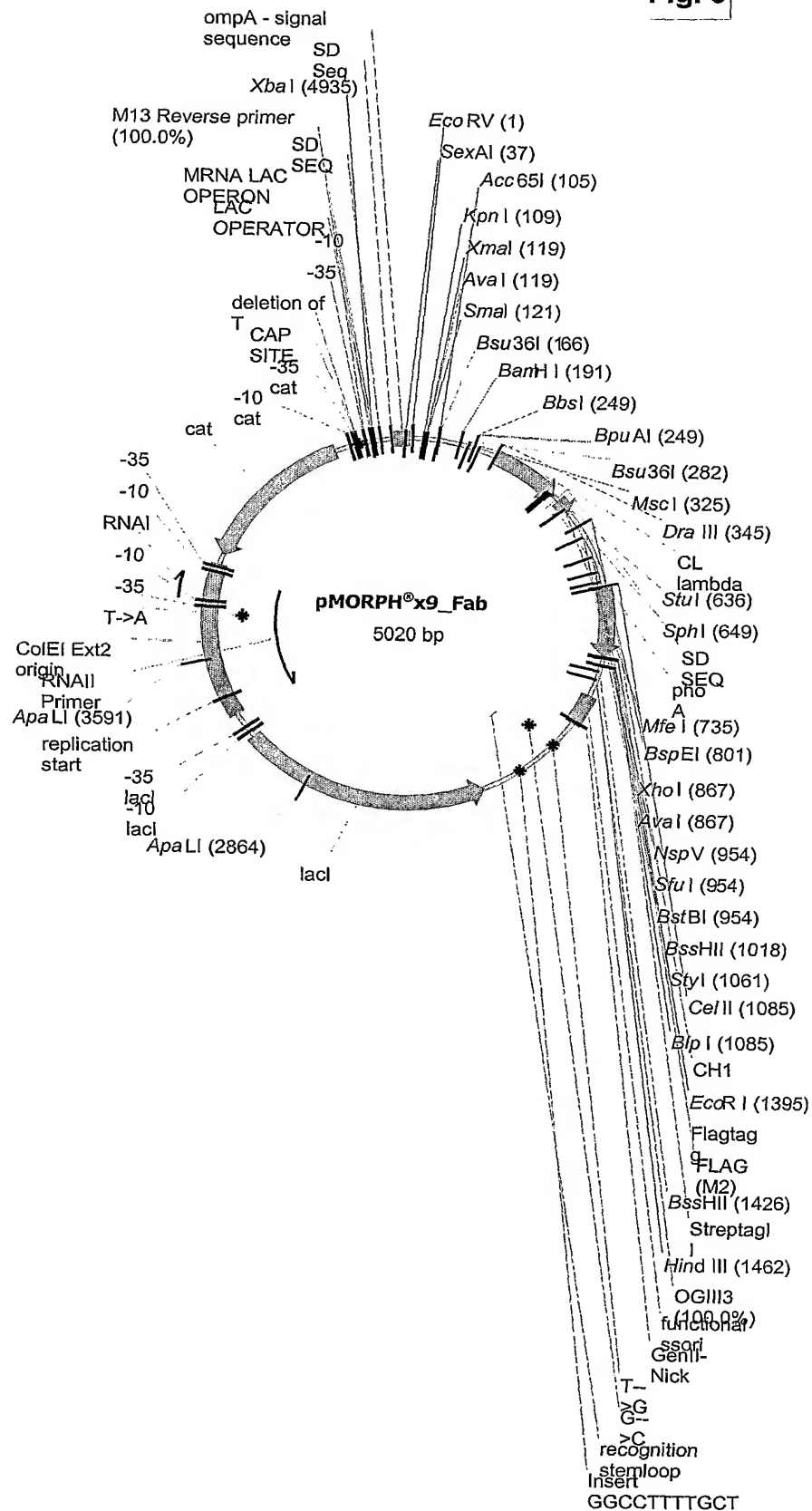
14/43

**Fig. 2 cont.**

CTCGCCTATT GTTAAAGTGT GTCCTTTGTC GATACTGGTA CTAATGCTTA  
lacZ'

4151 ~  
T  
A

**Fig. 3**



16/43

Fig. 3 cont.

	EcoRV				SexAI
	~~~~~				~~~~~
1	ATCGTGCTGA	CCCAGCCGCC	TTCAGTGAGT	GGCGCACCAG	GTCAGCGTGT
	TAGCACGACT	GGGTCGGCGG	AAGTCACTCA	CCGCGTGGTC	CAGTCGCACA
51	GACCATCTCG	TGTAGCGGCA	GCAGCAGCAA	CATTGGCAGC	AACTATGTGA
	CTGGTAGAGC	ACATCGCCGT	CGTCGTCGTT	GTAACCGTCG	TTGATACACT
		XmaI			
		~~~~~			
	KpnI	SmaI			
	~~~~~	~~~~~			
	Acc65I	AvaI			
	~~~~~	~~~~~			
101	GCTGGTACCA	GCAGTTGCCC	GGGACGGCGC	CGAAACTGCT	GATTTATGAT
	CGACCATGGT	CGTCAACGGG	CCCTGCCGCG	GCTTTGACGA	CTAAATACTA
		Bsu36I		BamHI	
		~~~~~		~~~~~	
151	AACAACCAGC	GTCCCTCAGG	CGTGCCGGAT	CGTTTTAGCG	GATCCAAAAG
	TTGTTGGTCG	CAGGGAGTCC	GCACGGCCTA	GCAAAATCGC	CTAGGTTTTT
				BpuAI	
				~~~~~	
				BbsI	
				~~~~~	
201	CGGCACCAGC	GCGAGCCTTG	CGATTACGGG	CCTGCAAAGC	GAAGACGAAG
	GCCGTGGTCG	CGCTCGGAAC	GCTAATGCCC	GGACGTTTCG	CTTCTGCTTC
			Bsu36I		
			~~~~~		
251	CGGATTATTA	TTGCCAGAGC	TATGACATGC	CTCAGGCTGT	GTTTGGCGGC
	GCCTAATAAT	AACGGTCTCG	ATACTGTACG	GAGTCCGACA	CAAACCGCCG
		MscI		DraIII	
		~~~~~		~~~~~	
301	GGCACGAAGT	TTAACCGTTC	TTGGCCAGCC	GAAAGCCGCA	CCGAGTGTGA
	CCGTGCTTCA	AATTGGCAAG	AACCGGTCGG	CTTTCGGCGT	GGCTCACACT
351	CGCTGTTTCC	GCCGAGCAGC	GAAGAATTGC	AGGCGAACAA	AGCGACCCTG
	GCGACAAAGG	CGGCTCGTCG	CTTCTTAACG	TCCGCTTGTT	TCGCTGGGAC
401	GTGTGCCTGA	TTAGCGACTT	TTATCCGGGA	GCCGTGACAG	TGGCCTGGAA
	CACACGGACT	AATCGCTGAA	AATAGGCCCT	CGGCACTGTC	ACCGGACCTT
451	GGCAGATAGC	AGCCCCGTCA	AGGCGGGAGT	GGAGACCACC	ACACCCTCCA
	CCGTCTATCG	TCGGGGCAGT	TCCGCCCTCA	CCTCTGGTGG	TGTGGGAGGT
501	AACAAAGCAA	CAACAAGTAC	GCGGCCAGCA	GCTATCTGAG	CCTGACGCCT
	TTGTTTCGTT	GTTGTTCATG	CGCCGGTTCG	CGATAGACTC	GGACTGCGGA
551	GAGCAGTGGA	AGTCCCACAG	AAGCTACAGC	TGCCAGGTCA	CGCATGAGGG
	CTCGTCACCT	TCAGGGTGTC	TTCGATGTCG	ACGGTCCAGT	GCGTACTCCC

17/43

Fig. 3 cont.

				StuI	SphI
				~~~~~	~~~~~
601	GAGCACCGTG	GAAAAAACCG	TTGCGCCGAC	TGAGGCCTGA	TAAGCATGCG
	CTCGTGGCAC	CTTTTTTGGC	AACGCGGCTG	ACTCCGGACT	ATTCGTACGC
651	TAGGAGAAAA	TAAAATGAAA	CAAAGCACTA	TTGCACTGGC	ACTCTTACCG
	ATCCTCTTTT	ATTTTACTTT	GTTTCGTGAT	AACGTGACCG	TGAGAATGGC
				MfeI	
				~~~~~	
701	TTGCTCTTCA	CCCCTGTTAC	CAAAGCCCAG	GTGCAATTGA	AAGAAAGCGG
	AACGAGAAGT	GGGACAATG	GTTTCGGGTC	CACGTTAAC	TTCTTTCGCG
					BspEI
					~
751	CCCGGCCCTG	GTGAAACCGA	CCCAAACCCT	GACCCTGACC	TGTACCTTTT
	GGGCCGGGAC	CACTTTGGCT	GGGTTTGGGA	CTGGGACTGG	ACATGGAAAA
					BspEI
					~~~~~
801	CCGGATTTAG	CCTGTCCACG	TCTGGCGTTG	GCGTGGGCTG	GATTCGCCAG
	GGCCTAAATC	GGACAGGTGC	AGACCGCAAC	CGCACCCGAC	CTAAGCGGTC
					XhoI
					~~~~~
					AvaI
					~~~~~
851	CCGCCTGGGA	AAGCCCTCGA	GTGGCTGGCT	CTGATTGATT	GGGATGATGA
	GGCGGACCC	TTCGGGAGCT	CACCGACCGA	GACTAACTAA	CCCTACTACT
901	TAAGTATTAT	AGCACCAGCC	TGAAAACGCG	TCTGACCATT	AGCAAAGATA
	ATTCATAATA	TCGTGGTCGG	ACTTTTGCGC	AGACTGGTAA	TCGTTTCTAT
					BstBI
					~~~~~
					SfuI
					~~~~~
					NspV
					~~~~~
951	CTTCGAAAAA	TCAGGTGGTG	CTGACTATGA	CCAACATGGA	CCCGGTGGAT
	GAAGCTTTTT	AGTCCACCAC	GACTGATACT	GGTTGTACCT	GGGCCACCTA
					BssHII
					~~~~~
1001	ACGGCCACCT	ATTATTGCGC	GCGTTCTCCT	CGTTATCGTG	GTGCTTTTGA
	TGCCGGTGGA	TAATAACGCG	CGCAAGAGGA	GCAATAGCAC	CACGAAAAC
					BlpI
					~~~~~
					CelII
					~~~~~
					StyI
					~~~~~
1051	TTATTGGGGC	CAAGGCACCC	TGGTGACGGT	TAGCTCAGCG	TCGACCAAAG
	AATAACCCCG	GTTCCGTGGG	ACCACTGCCA	ATCGAGTCGC	AGCTGGTTTC

18/43

Fig. 3 cont.

1101	GTCCAAGCGT	GTTTCCGCTG	GCTCCGAGCA	GCAAAAGCAC	CAGCGGCGGC
	CAGGTTCGCA	CAAAGGCGAC	CGAGGCTCGT	CGTTTTTCGTG	GTCGCCGCCG
1151	ACGGCTGCCC	TGGGCTGCCT	GGTTAAAGAT	TATTTCCCGG	AACCAGTCAC
	TGCCGACGGG	ACCCGACGGA	CCAATTTCTA	ATAAAGGGCC	TTGGTCAGTG
1201	CGTGAGCTGG	AACAGCGGGG	CGCTGACCAG	CGGCGTG CAT	ACCTTTCCGG
	GCACTCGACC	TTGTCGCCCC	GCGACTGGTC	GCCGCACGTA	TGGAAAGGCC
1251	CGGTGCTGCA	AAGCAGCGGC	CTGTATAGCC	TGAGCAGCGT	TGTGACCGTG
	GCCACGACGT	TTCGTCGCCG	GACATATCGG	ACTCGTCGCA	AACTTGGCAC
1301	CCGAGCAGCA	GCTTAGGCAC	TCAGACCTAT	ATTTGCAACG	TGAACCATAA
	GGCTCGTCGT	CGAATCCGTG	AGTCTGGATA	TAAACGTTGC	ACTTGGTATT
				EcoRI	
				~~~~~	
1351	ACCGAGCAAC	ACCAAAGTGG	ATAAAAAAGT	GGAACCGAAA	AGCGAATTCTG
	TGGCTCGTTG	TGGTTTCACC	TATTTTTTCA	CCTTGGCTTT	TCGCTTAAGC
			BssHII		
			~~~~~		
1401	ACTATAAAGA	TGACGATGAC	AAAGGCGCGC	CGTGGAGCCA	CCCGCAGTTT
	TGATATTTCT	ACTGCTACTG	TTTCCGCGCG	GCACCTCGGT	GGGCGTCAAA
			HindIII		
			~~~~~		
1451	GAAAAATGAT	AAGCTTGACC	TGTGAAGTGA	AAAATGGCGC	AGATTGTGCG
	CTTTTTACTA	TTCGAACTGG	ACACTTCACT	TTTTACCGCG	TCTAACACGC
			OGIII3	100.0%	
			=====		
1501	ACATTTTTTTT	TGTCTGCCGT	TTAATTAAAG	GGGGGGGGGG	GCCGGCCTGG
	TGTAAAAAAA	ACAGACGGCA	AATTAATTTC	CCCCCCCCCC	CGGCCGGACC
1551	GGGGGGGTGT	ACATGAAATT	GTAAACGTTA	ATATTTTGTT	AAAATTCGCG
	CCCCCCCACA	TGTACTTTAA	CATTTGCAAT	TATAAAACAA	TTTTAAGCGC
1601	TTAAATTTTTT	GTTAAATCAG	CTCATTTTTT	AACCAATAGG	CCGAAATCGG
	AATTTAAAAA	CAATTTAGTC	GAGTAAAAAA	TTGGTTATCC	GGCTTTAGCC
1651	CAAAATCCCT	TATAAATCAA	AAGAATAGAC	CGAGATAGGG	TTGAGTGTTG
	GTTTTAGGGA	ATATTTAGTT	TTCTTATCTG	GCTCTATCCC	AACTCACAAAC
1701	TTCCAGTTTG	GAACAAGAGT	CCACTATTAA	AGAACGTGGA	CTCCAACGTC
	AAGGTCAAAC	CTTGTTCTCA	GGTGATAATT	TCTTGACACT	GAGGTTGCAG
1751	AAAGGGCGAA	AAACCGTCTA	TCAGGGCGAT	GGCCCACTAC	GAGAACCATC
	TTTCCCGCTT	TTTGGCAGAT	AGTCCCAGTA	CCGGGTGATG	CTCTTGGTAG
1801	ACCCTAATCA	AGTTTTTTTG	GGTCGAGGTG	CCGTAAAGCA	CTAAATCGGA
	TGGGATTAGT	TCAAAAACC	CCAGCTCCAC	GGCATTTTCGT	GATTTAGCCT

19/43

Fig. 3 cont. |

1851	ACCCTAAAGG	GAGCCCCCGA	TTTAGAGCTT	GACGGGGAAA	GCCGGCGAAC
	TGGGATTTC	CTCGGGGGCT	AAATCTCGAA	CTGCCCTTT	CGGCCGCTTG
1901	GTGGCGAGAA	AGGAAGGGAA	GAAAGCGAAA	GGAGCGGGCG	CTAGGGCGCT
	CACCGCTCTT	TCCTTCCTT	CTTTCGCTTT	CCTCGCCCGC	GATCCCGCGA
1951	GGCAAGTGTA	GCGGTCACGC	TGCGCGTAAC	CACCACACCC	GCCGCGCTTA
	CCGTTACAT	CGCCAGTGCG	ACGCGCATTG	GTGGTGTGGG	CGGCGCGAAT
2001	ATGCGCCGCT	ACAGGGCGCG	TGCTAGACTA	GTGTTTAAAC	CGGACCGGGG
	TACGCGGCGA	TGTCCCGCGC	ACGATCTGAT	CACAAATTTG	GCCTGGCCCC
2051	GGGGGCTTAA	GTGGGCTGCA	AAACAAAACG	GCCTCCTGTC	AGGAAGCCGC
	CCCCCGAATT	CACCCGACGT	TTTGTTTTGC	CGGAGGACAG	TCCTTCGGCG
2101	TTTTATCGGG	TAGCCTCACT	GCCCGCTTTC	CAGTCGGGAA	ACCTGTCGTG
	AAAATAGCCC	ATCGGAGTGA	CGGGCGAAAG	GTCAGCCCTT	TGGACAGCAC
2151	CCAGCTGCAT	CAGTGAATCG	GCCAACGCGC	GGGAGAGGGC	GGTTTGCGTA
	GGTCGACGTA	GTCACCTAGC	CGGTTGCGCG	CCCCTCTCCG	CCAAACGCAT
2201	TTGGGAGCCA	GGGTGGTTTT	TCTTTTCACC	AGTGAGACGG	GCAACAGCTG
	AACCCTCGGT	CCCACCAAAA	AGAAAAGTGG	TCACTCTGCC	CGTTGTGCGC
2251	ATTGCCCTTC	ACCGCCTGGC	CCTGAGAGAG	TTGCAGCAAG	CGGTCCACGC
	TAACGGGAAG	TGGCGGACCG	GGACTCTCTC	AACGTCGTTT	GCCAGGTGCG
2301	TGGTTTGCCC	CAGCAGGCGA	AAATCCTGTT	TGATGGTGGT	CAGCGGCGGG
	ACCAAACGGG	GTCGTCCGCT	TTTAGGACAA	ACTACCACCA	GTCGCCGCCC
2351	ATATAACATG	AGCTGTCCTC	GGTATCGTCG	TATCCCACTA	CCGAGATGTC
	TATATTGTAC	TCGACAGGAG	CCATAGCAGC	ATAGGGTGAT	GGCTCTACAG
2401	CGCACCAACG	CGCAGCCCCG	ACTCGGTAAT	GGCACGCATT	GCGCCCAGCG
	GCGTGTTGCT	GCGTCGGGCC	TGAGCCATTA	CCGTGCGTAA	CGCGGGTCGC
2451	CCATCTGATC	GTTGGCAACC	AGCATCGCAG	TGGGAACGAT	GCCCTCATTC
	GGTAGACTAG	CAACCGTTGG	TCGTAGCGTC	ACCCTTGCTA	CGGGAGTAAG
2501	AGCATTTGCA	TGGTTTGTTG	AAAACCGGAC	ATGGCACTCC	AGTCGCCTTC
	TCGTAAACGT	ACCAAACAAC	TTTTGGCCTG	TACCGTGAGG	TCAGCGGAAG
2551	CCGTTCCGCT	ATCGGCTGAA	TTTGATTGCG	AGTGAGATAT	TTATGCCAGC
	GGCAAGGCGA	TAGCCGACTT	AAACTAACGC	TCACTCTATA	AATACGGTCC
2601	CAGCCAGACG	CAGACGCGCC	GAGACAGAAC	TTAATGGGCC	AGCTAACAGC
	GTCGGTCTGC	GTCTGCGCGG	CTCTGTCTTG	AATTACCCGG	TCGATTGTGC
2651	GCGATTTGCT	GGTGGCCCAA	TGCGACCAGA	TGCTCCACGC	CCAGTCGCGT
	CGCTAAACGA	CCACCGGGTT	ACGCTGGTCT	ACGAGGTGCG	GGTCAGCGCA
2701	ACCGTCCTCA	TGGGAGAAAA	TAATACTGTT	GATGGGTGTC	TGGTCAGAGA
	TGGCAGGAGT	ACCCTCTTTT	ATTATGACAA	CTACCCACAG	ACCAGTCTCT

20/43

Fig. 3 cont.

2751 CATCAAGAAA TAACGCCGGA ACATTAGTGC AGGCAGCTTC CACAGCAATA  
GTAGTTCTTT ATTGCGGCCT TGTAATCACG TCCGTCGAAG GTGTCGTTAT

2801 GCATCCTGGT CATCCAGCGG ATAGTTAATA ATCAGCCAC TGACACGTTG  
CGTAGGACCA GTAGGTCGCC TATCAATTAT TAGTCGGGTG ACTGTGCAAC

ApaLI

~~~~~

2851 CGCGAGAAGA TTGTGCACCG CCGCTTTACA GGCTTCGACG CCGCTTCGTT
GCGCTCTTCT AACACGTGGC GGCGAAATGT CCGAAGCTGC GGCGAAGCAA

2901 CTACCATCGA CACGACCACG CTGGCACCCA GTTGATCGGC GCGAGATTTA
GATGGTAGCT GTGCTGGTGC GACCGTGGGT CAACTAGCCG CGCTCTAAAT

2951 ATCGCCGCGA CAATTTGCGA CGGCGCGTGC AGGGCCAGAC TGGAGGTGGC
TAGCGGCGCT GTTAAACGCT GCCGCGCACG TCCCGGTCTG ACCTCCACCG

3001 AACGCCAATC AGCAACGACT GTTTGCCCGC CAGTTGTTGT GCCACGCGGT
TTGCGGTTAG TCGTTGCTGA CAAACGGGCG GTCAACAACA CGGTGCGCCA

3051 TAGGAATGTA ATTCAGCTCC GCCATCGCCG CTTCCACTTT TTCCCGCGTT
ATCCTTACAT TAAGTCGAGG CGGTAGCGGC GAAGGTGAAA AAGGGCGCAA

3101 TTCGCAGAAA CGTGGCTGGC CTGGTTCACC ACGCGGGAAA CGGTCTGATA
AAGCGTCTTT GCACCGACCG GACCAAGTGG TGCGCCCTTT GCCAGACTAT

3151 AGAGACACCG GCATACTCTG CGACATCGTA TAACGTTACT GGTTCACAT
TCTCTGTGGC CGTATGAGAC GCTGTAGCAT ATTGCAATGA CCAAAGTGTA

3201 TCACCACCCT GAATTGACTC TCTTCCGGGC GCTATCATGC CATAACGCGA
AGTGGTGGGA CTTAACTGAG AGAAGGCCCG CGATAGTACG GTATGGCGCT

3251 AAGGTTTTGC GCCATTCGAT GCTAGCCATG TGAGCAAAAG GCCAGCAAAA
TTCCAAAACG CGGTAAGCTA CGATCGGTAC ACTCGTTTTT CGGTCGTTTT

3301 GGCCAGGAAC CGTAAAAAGG CCGCGTTGCT GGCCTTTTTT CATAGGCTCC
CCGGTCCCTG GCATTTTTTC GGCGCAACGA CCGCAAAAAG GTATCCGAGG

3351 GCCCCCTGA CGAGCATCAC AAAAATCGAC GCTCAAGTCA GAGGTGGCGA
CGGGGGGACT GCTCGTAGTG TTTTATAGCTG CGAGTTCAGT CTCCACCGCT

3401 AACCCGACAG GACTATAAAG ATACCAGGCG TTTCCCCCTG GAAGCTCCCT
TTGGGCTGTC CTGATATTTC TATGGTCCGC AAAGGGGGAC CTTCGAGGGA

3451 CGTGCGCTCT CCTGTTCCGA CCCTGCCGCT TACCGGATAC CTGTCCGCCT
GCACGCGAGA GGACAAGGCT GGGACGGCGA ATGGCCTATG GACAGGCGGA

3501 TTCTCCCTTC GGGAAGCGTG GCGCTTTCTC ATAGCTCACG CTGTAGGTAT
AAGAGGGAAG CCCTTCGCAC CGCGAAAGAG TATCGAGTGC GACATCCATA

ApaLI

~~~~~

3551 CTCAGTTCGG TGTAGGTCGT TCGCTCCAAG CTGGGCTGTG TGCACGAACC  
GAGTCAAGCC ACATCCAGCA AGCGAGGTTT GACCCGACAC ACGTGCTTGG



21/43

Fig. 3 cont.

3601	CCCCGTTTCAG GGGGCAAGTC	CCCGACCGCT GGGCTGGCGA	GCGCCTTATC CGCGGAATAG	CGGTAACATAT GCCATTGATA	CGTCTTGAGT GCAGAACTCA
3651	CCAACCCGGT GGTTGGGCCA	AAGACACGAC TTCTGTGCTG	TTATCGCCAC AATAGCGGTG	TGGCAGCAGC ACCGTCGTCG	CACTGGTAAC GTGACCATTG
3701	AGGATTAGCA TCCTAATCGT	GAGCGAGGTA CTCGCTCCAT	TGTAGGCGGT ACATCCGCCA	GCTACAGAGT CGATGTCTCA	TCTTGAAGTG AGAACTTCAC
3751	GTGGCCTAAC CACCGGATTG	TACGGCTACA ATGCCGATGT	CTAGAAGAAC GATCTTCTTG	AGTATTTGGT TCATAAACCA	ATCTGCGCTC TAGACGCGAG
3801	TGCTGTAGCC ACGACATCGG	AGTTACCTTC TCAATGGAAG	GGAAAAAGAG CCTTTTTTCTC	TTGGTAGCTC AACCATCGAG	TTGATCCGGC AACTAGGCCG
3851	AAACAAACCA TTTGTTTGGT	CCGCTGGTAG GGCGACCATC	CGGTGGTTTTT GCCACCAAAA	TTTGTTTGCA AAACAAACGT	AGCAGCAGAT TCGTGCTCTA
3901	TACGCGCAGA ATGCGCGTCT	AAAAAAGGAT TTTTTTCCTA	CTCAAGAAGA GAGTTCTTCT	TCCTTTGATC AGGAAACTAG	TTTTCTACGG AAAAGATGCC
3951	GGTCTGACGC CCAGACTGCG	TCAGTGGAAC AGTCACCTTG	GAAAACTCAC CTTTTGAGTG	GTTAAGGGAT CAATTCCCTA	TTTGGTCAGA AAACCAGTCT
4001	TCTAGCACCA AGATCGTGGT	GGCGTTTAAG CCGCAAATTC	GGCACCAATA CCGTGGTTAT	ACTGCCTTAA TGACGGAATT	AAAAATTACG TTTTTAATGC
4051	CCCCGCCCTG GGGGCGGGAC	CCACTCATCG GGTGAGTAGC	CAGTACTGTT GTCATGACAA	GTAATTCATT CATTAAAGTAA	AAGCATTCTG TTCGTAAGAC
4101	CCGACATGGA GGCTGTACCT	AGCCATCACA TCGGTAGTGT	AACGGCATGA TTGCCGTACT	TGAACCTGAA ACTTGGACTT	TCGCCAGCGG AGCGGTCGCC
4151	CATCAGCACC GTAGTCGTGG	TTGTGCGCCTT AACAGCGGAA	GCGTATAATA CGCATATTAT	TTTGCCCATATA AAACGGGTAT	GTGAAAACGG CACTTTTGCC
4201	GGGCGAAGAA CCCCTTCTT	GTTGTCCATA CAACAGGTAT	TTGGCTACGT AACCGATGCA	TTAAATCAAA AATTTAGTTT	ACTGGTGAAA TGACCACTTT
4251	CTCACCAGG GAGTGGGTCC	GATTGGCTGA CTAACCGACT	GACGAAAAAC CTGCTTTTGTG	ATATTCTCAA TATAAGAGTT	TAAACCCTTT ATTTGGGAAA
4301	AGGGAAATAG TCCCTTTATC	GCCAGGTTTT CGGTCCAAAA	CACCGTAACA GTGGCATTGT	CGCCACATCT GCGGTGTAGA	TGCGAATATA ACGCTTATAT
4351	TGTGTAGAAA ACACATCTTT	CTGCCGGAAA GACGGCCTTT	TCGTGCTGGT AGCAGCACCA	ATTCACTCCA TAAGTGAGGT	GAGCGATGAA CTCGCTACTT
4401	AACGTTTCAG TTGCAAAGTC	TTTGCTCATG AAACGAGTAC	GAAAACGGTG CTTTTGCCAC	TAACAAGGGT ATTGTTCCCA	GAACACTATC CTTGTTGATAG
4451	CCATATCACC GGTATAGTGG	AGCTCACCGT TCGAGTGCA	CTTTCATTGC GAAAGTAACG	CATACGGAAC GTATGCCTTG	TCCGGGTGAG AGGCCCACTC

22/43

Fig. 3 cont.

4501	CATTCATCAG	GCGGGCAAGA	ATGTGAATAA	AGGCCGGATA	AAACTTGTGC
	GTAAGTAGTC	CGCCCGTTCT	TACACTTATT	TCCGGCCTAT	TTTGAACACG
4551	TTATTTTTCT	TTACGGTCTT	TAAAAAGGCC	GTAATATCCA	GCTGAACGGT
	AATAAAAAGA	AATGCCAGAA	ATTTTTCGG	CATTATAGGT	CGACTTGCCA
4601	CTGGTTATAG	GTACATTGAG	CAACTGACTG	AAATGCCTCA	AAATGTTCTT
	GACCAATATC	CATGTAATC	GTTGACTGAC	TTTACGGAGT	TTTACAAGAA
4651	TACGATGCCA	TTGGGATATA	TCAACGGTGG	TATATCCAGT	GATTTTTTTC
	ATGCTACGGT	AACCCTATAT	AGTTGCCACC	ATATAGGTCA	CTAAAAAAG
4701	TCCATTTTATAG	CTTCCTTAGC	TCCTGAAAAT	CTCGATAACT	CAAAAAATAC
	AGGTAAAATC	GAAGGAATCG	AGGACTTTTA	GAGCTATTGA	GTTTTTTATG
4751	GCCCGGTAGT	GATCTTATTT	CATTATGGTG	AAAGTTGGAA	CCTCACCCGA
	CGGGCCATCA	CTAGAATAAA	GTAATACCAC	TTTCAACCTT	GGAGTGGGCT
4801	CGTCTAATGT	GAGTTAGCTC	ACTCATTAGG	CACCCCAGGC	TTTACACTTT
	GCAGATTACA	CTCAATCGAG	TGAGTAATCC	GTGGGGTCCG	AAATGTGAAA
4851	ATGCTTCCGG	CTCGTATGTT	GTGTGGAATT	GTGAGCGGAT	AACAATTTCA
	TACGAAGGCC	GAGCATACAA	CACACCTTAA	CACTCGCCTA	TTGTTAAAGT
	M13 Reverse primer 100.0%		XbaI		
	=====		~~~~~		
4901	CACAGGAAAC	AGCTATGACC	ATGATTACGA	ATTTCTAGAT	AACGAGGGCA
	GTGTCCTTTG	TCGATACTGG	TACTAATGCT	TAAAGATCTA	TTGCTCCCGT
4951	AAAAATGAAA	AAGACAGCTA	TCGCGATTGC	AGTGGCACTG	GCTGGT'TTCG
	TTTTTACTTT	TTCTGTCGAT	AGCGCTAACG	TCACCGTGAC	CGACCAAAGC
		EcoRV			
		~~~			
5001	CTACCGTAGC	GCAGGCCGAT			
	GATGGCATCG	CGTCCGGCTA			

24/43

Fig. 4a cont.

Framework 3										CDR 3										Framework 4																																	
6										9										10																																	
8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9																						
BamHI										BstI										MscI										BstXI																							
V	P	A	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	E	P	E	D	F	A	V	Y	Y	C	Q	Q	V	Y	N	P	P	-	V	T	F	G	Q	G	T	K	V	E	I	K	R	T	
V	P	A	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	E	P	E	D	F	A	T	Y	Y	C	F	Q	L	Y	S	D	P	-	-	F	T	F	G	Q	G	T	K	V	E	I	K	R	T
V	P	A	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	E	P	E	D	F	A	T	Y	Y	C	Q	Q	L	S	S	F	P	-	-	P	T	F	G	Q	G	T	K	V	E	I	K	R	T

Framework 3										CDR 3										Framework 4																																										
6										8										9										10										11																						
9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	a	b	c	d	e	f	g	h	i	j	1	2	3	4	5	6	7	8	9	0	1	2	3																		
BstEII										NspV										EagI										BssHII										SstI										BspI												
Y	A	D	S	V	K	G	R	F	T	I	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	R	L	T	H	Y	A	R	Y	Y	R	Y	F	D	V	W	G	Q	G	T	L	V	T	V	S	S
Y	A	D	S	V	K	G	R	F	T	I	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	R	L	T	H	Y	A	R	Y	Y	R	Y	F	D	V	W	G	Q	G	T	L	V	T	V	S	S
Y	A	D	S	V	K	G	R	F	T	I	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	R	L	T	H	Y	A	R	Y	Y	R	Y	F	D	V	W	G	Q	G	T	L	V	T	V	S	S

Fig. 4b cont.

26/43

Framework 2										CDR 2										Framework 3																																																			
4										5										6										7										8																															
7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	BbsI																																			
SexAI										AseI										SanDI										BamHI																																									
CAG CAG AAG CCA GGT										CTA TTA ATT										TAT										GGC GCG AGC AGC CGT GCA ACT										GGG GTC CCG GCG CGT TTT AGC GGC TCT										GGA TCC										GGC ACG GAT TTT ACC CTG ACC ATT AGC AGC CTG GAA CCT										GAA GAC	
CAG CAG AAG CCA GGT										CTA TTA ATT										TAT										GGC GCG AGC AGC CGT GCA ACT										GGG GTC CCG GCG CGT TTT AGC GGC TCT										GGA TCC										GGC ACG GAT TTT ACC CTG ACC ATT AGC AGC CTG GAA CCT										GAA GAC	
CAG CAG AAG CCA GGT										CTA TTA ATT										TAT										GGC GCG AGC AGC CGT GCA ACT										GGG GTC CCG GCG CGT TTT AGC GGC TCT										GGA TCC										GGC ACG GAT TTT ACC CTG ACC ATT AGC AGC CTG GAA CCT										GAA GAC	
CAG CAG AAG CCA GGT										CTA TTA ATT										TAT										GGC GCG AGC AGC CGT GCA ACT										GGG GTC CCG GCG CGT TTT AGC GGC TCT										GGA TCC										GGC ACG GAT TTT ACC CTG ACC ATT AGC AGC CTG GAA CCT										GAA GAC	

Framework 2										CDR 2										Framework 3																									
1	2	3	4	5	6	7	8	9	0	1	2	a	b	c	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	a										
XhoI										BstEII										NspV																									
CCT	GGG	AAG	GGT	CTC	GAG	TGG	GTG	AGC	GGC	ATT	AGC	GGT	-	-	AGC	GGC	GGC	AGC	ACC	TAT	TAT	GCG	GAT	AGC	GTG	AAA	GGC	CGT	TTT	ACC	ATT	TCA	CGT	GAT	ATT	TCG	AAA	AAC	ACC	CTG	TAT	CTG	CAA	ATG	AAC
CCT	GGG	AAG	GGT	CTC	GAG	TGG	GTG	AGC	GGC	ATT	AGC	GGT	-	-	AGC	GGC	GGC	AGC	ACC	TAT	TAT	GCG	GAT	AGC	GTG	AAA	GGC	CGT	TTT	ACC	ATT	TCA	CGT	GAT	ATT	TCG	AAA	AAC	ACC	CTG	TAT	CTG	CAA	ATG	AAC
CCT	GGG	AAG	GGT	CTC	GAG	TGG	GTG	AGC	GGC	ATT	AGC	GGT	-	-	AGC	GGC	GGC	AGC	ACC	TAT	TAT	GCG	GAT	AGC	GTG	AAA	GGC	CGT	TTT	ACC	ATT	TCA	CGT	GAT	ATT	TCG	AAA	AAC	ACC	CTG	TAT	CTG	CAA	ATG	AAC

27/43

Fig. 4b cont.

CDR 3																	Framework 4																
3	4	5	6	7	8	9	0	1	2	3	4	5	a	b	6	7	8	9	0	1	2	3	4	5	6	7	8	9					
TTT	GCG	GTT	TAT	TAT	TGC	CAG	CAG	GTT	TAT	AAT	CCT	CCT					GTT	ACC	TTT	GGC	CAG	GGT	ACG	AAA	GTT	GAA	ATT	AAA	CGT	ACG			
TTT	GCG	ACT	TAT	TAT	TGC	TTT	CAG	CTT	TAT	TCT	GAT	CCT					TTT	ACC	TTT	GGC	CAG	GGT	ACG	AAA	GTT	GAA	ATT	AAA	CGT	ACG			
TTT	GCG	ACT	TAT	TAT	TGC	CAG	CAG	CTT	TCT	TCT	TTT	CCT					CCT	ACC	TTT	GGC	CAG	GGT	ACG	AAA	GTT	GAA	ATT	AAA	CGT	ACG			

28/43

Fig. 5

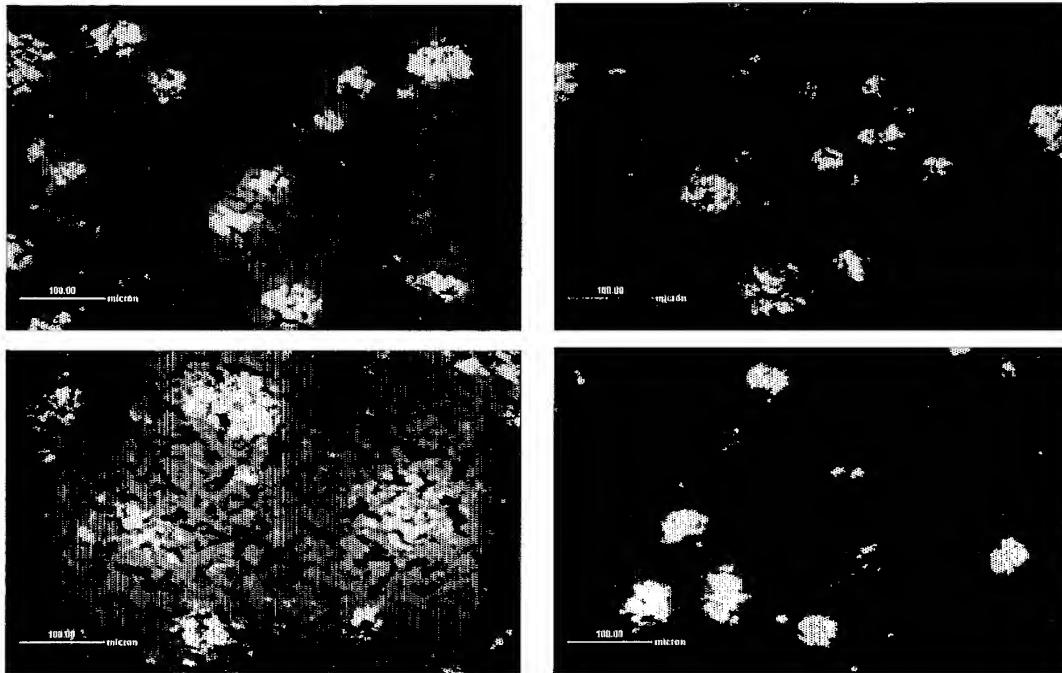


Fig. 6

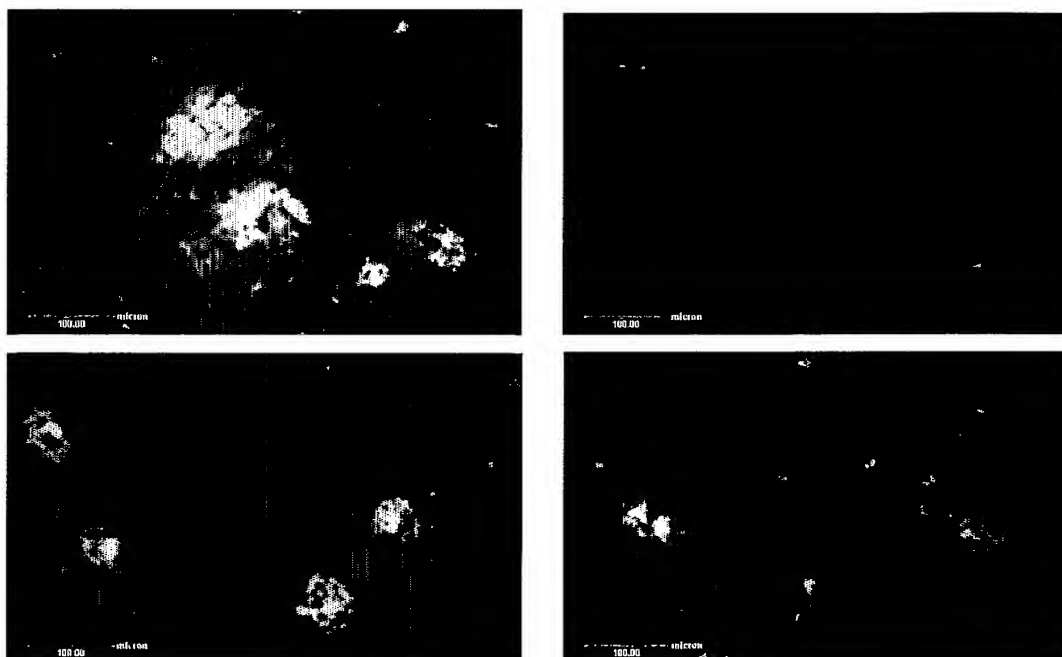
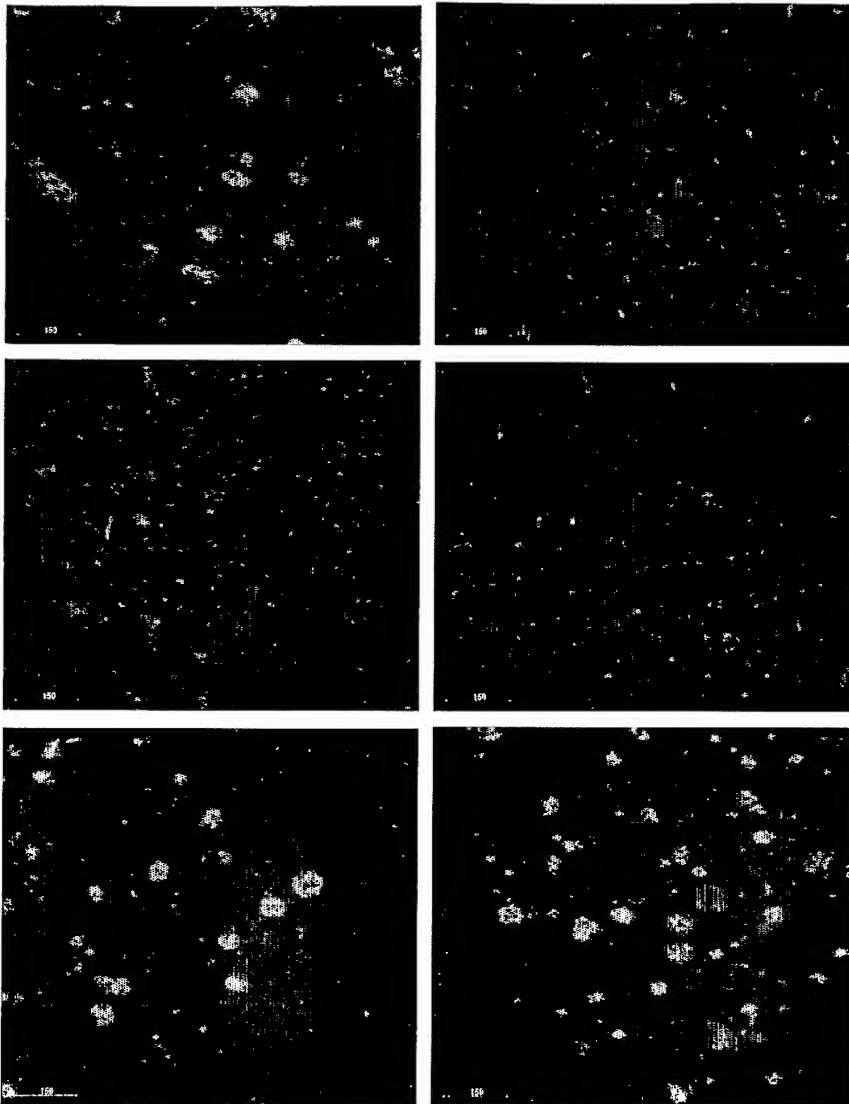
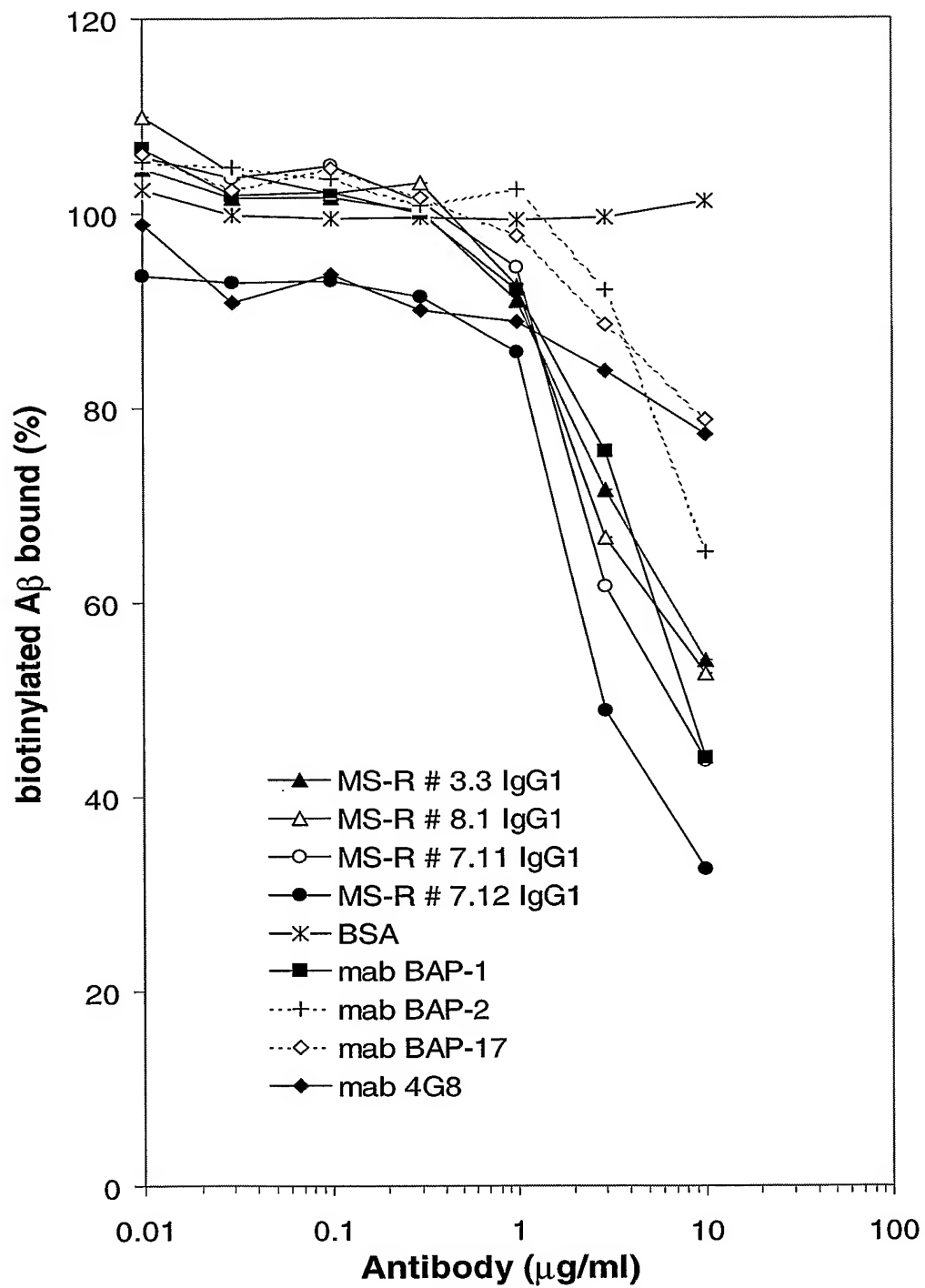


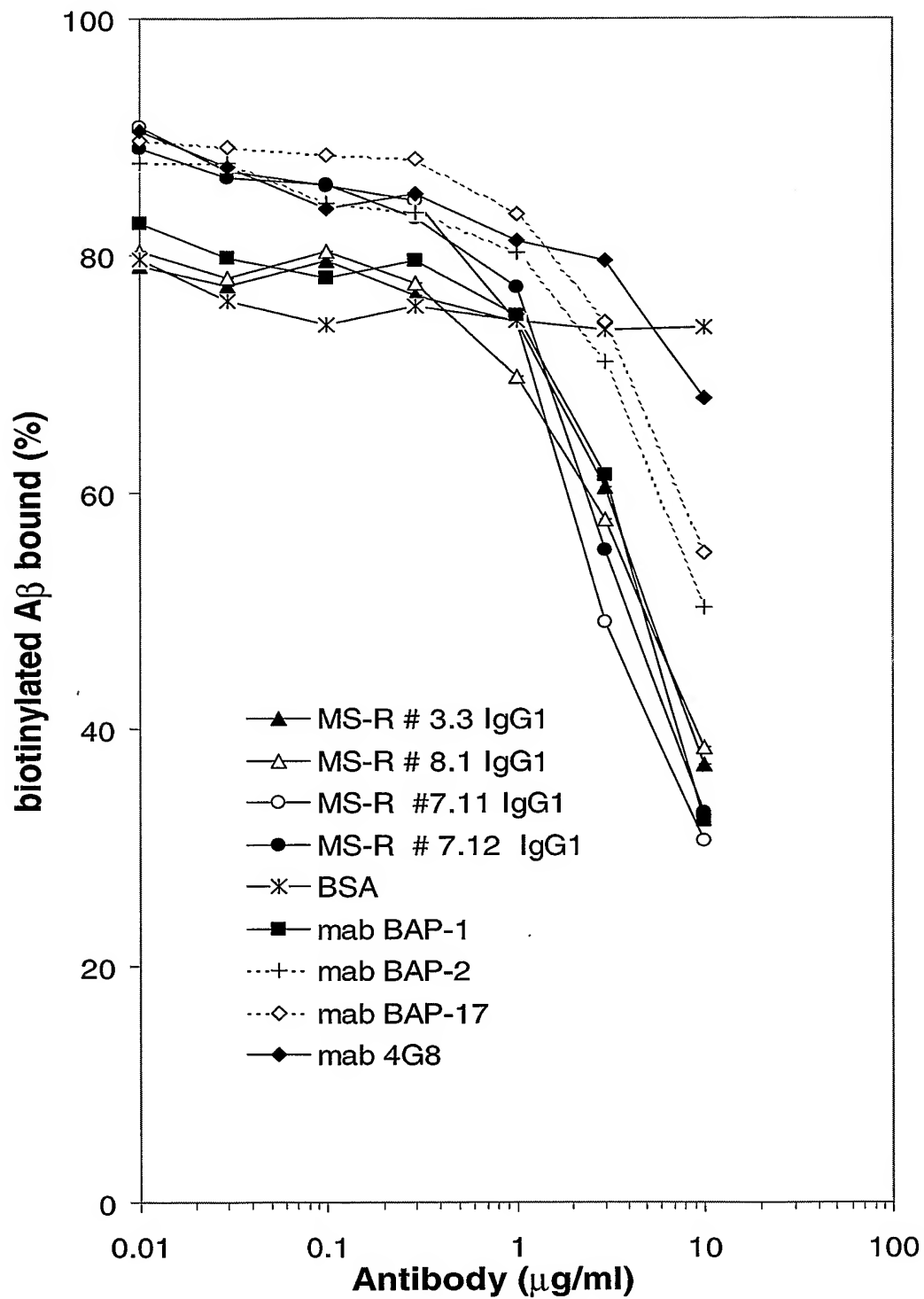
Fig. 7

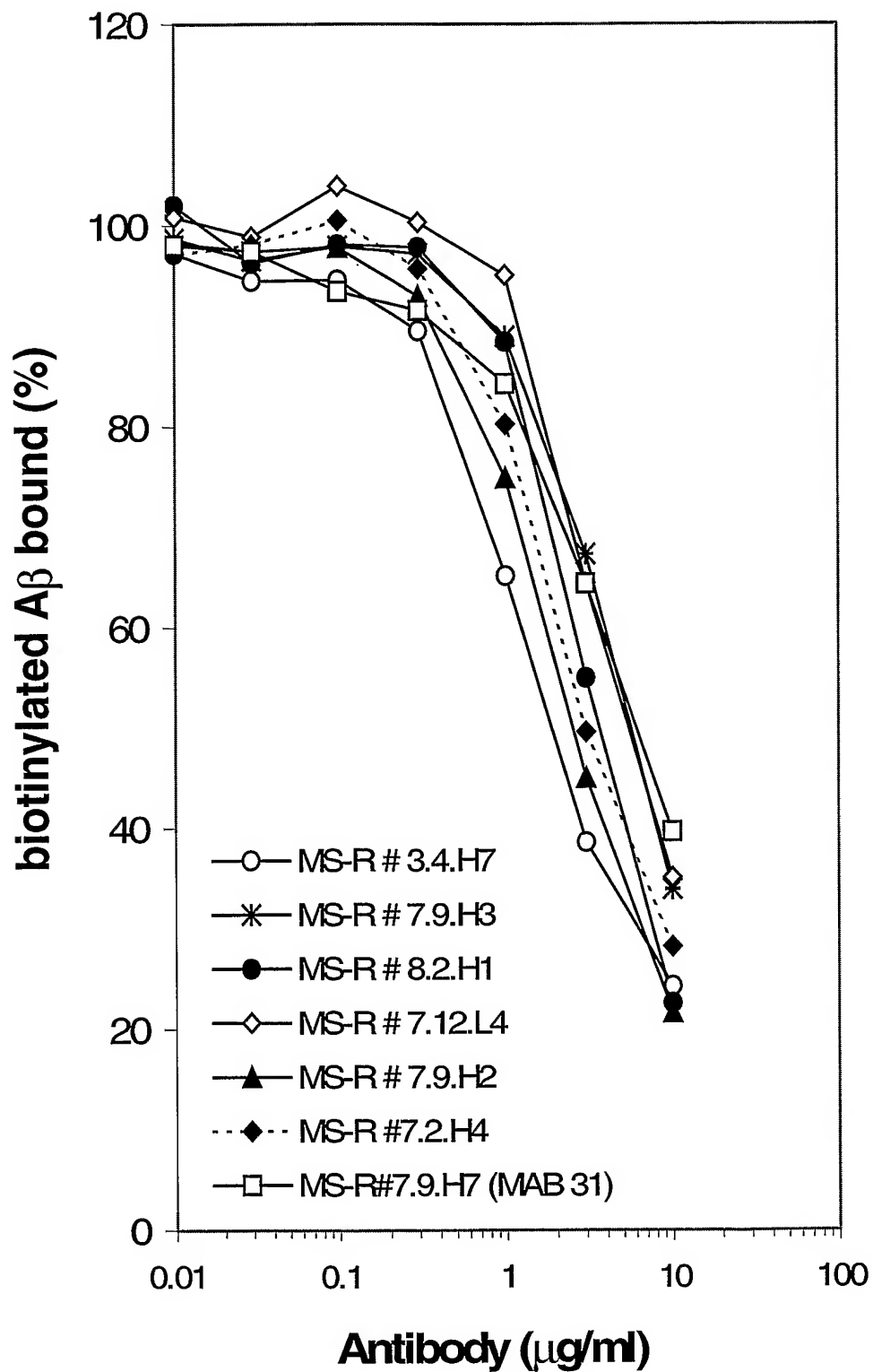


30/43

Fig. 8

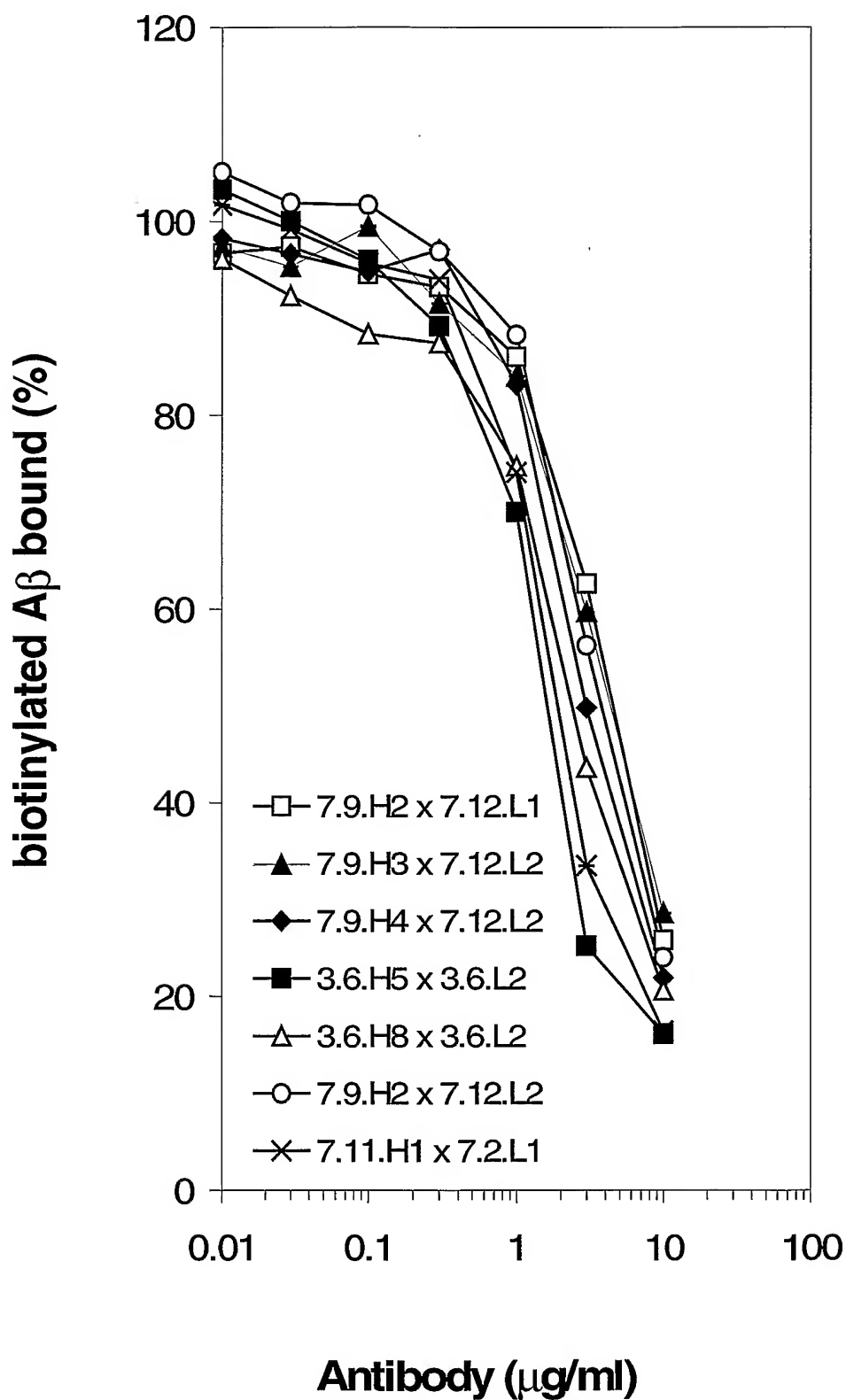


31/43
Fig. 9A

32/43
Fig. 9B

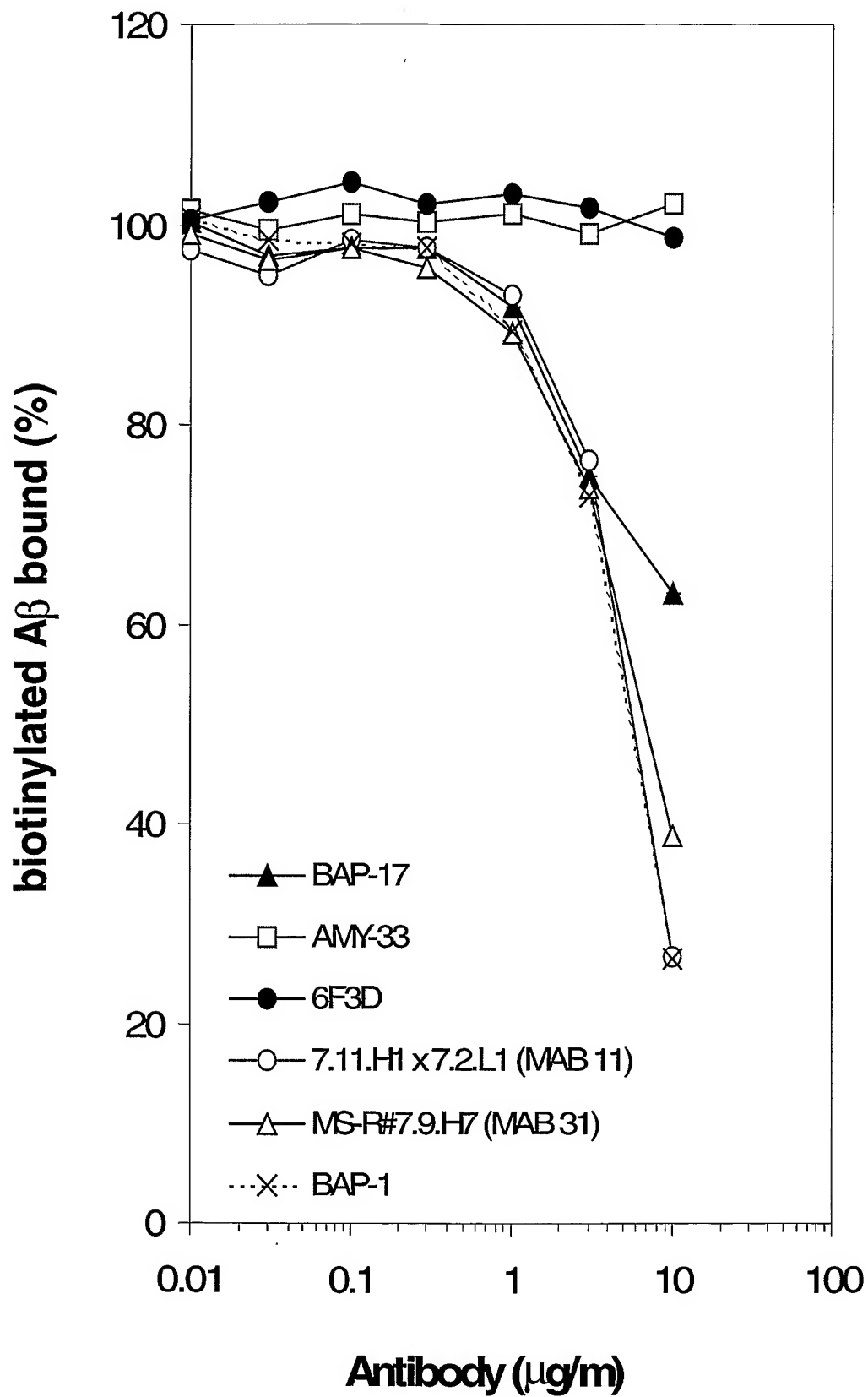
33/43

Fig. 9C



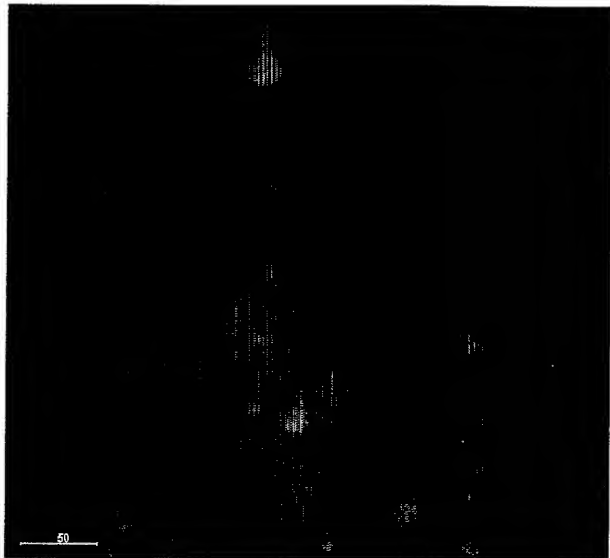
34/43

Fig. 9D



35/43
Fig. 10

A



B



C

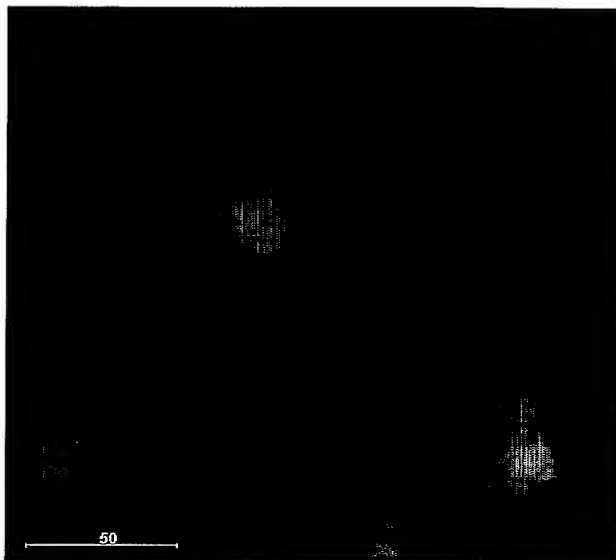


D

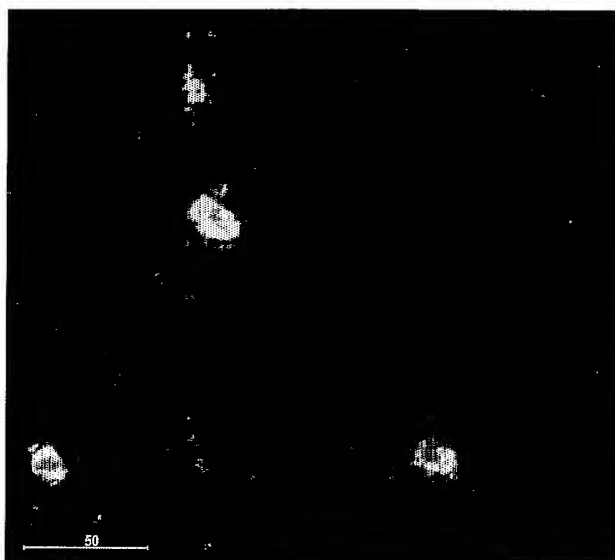


36/43
Fig. 11

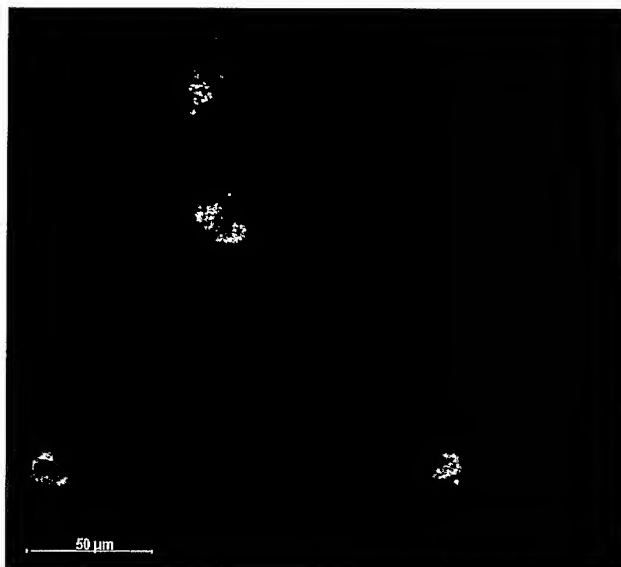
A



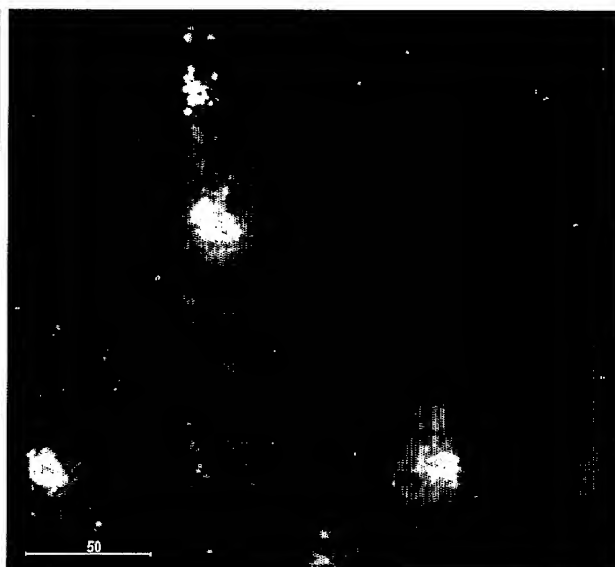
B



C

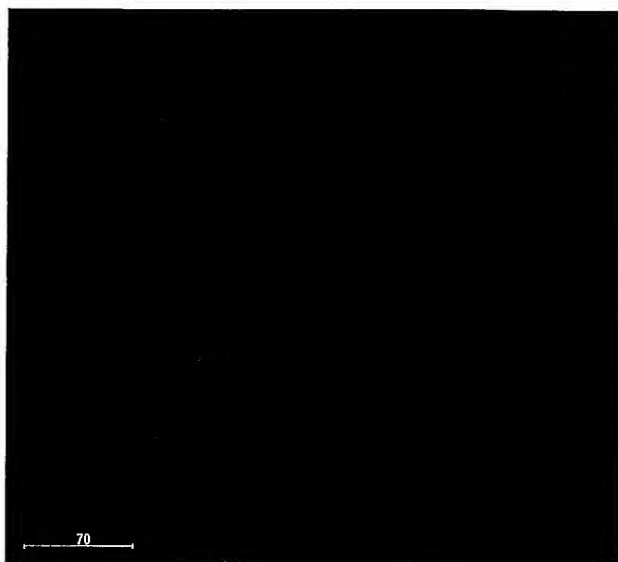


D

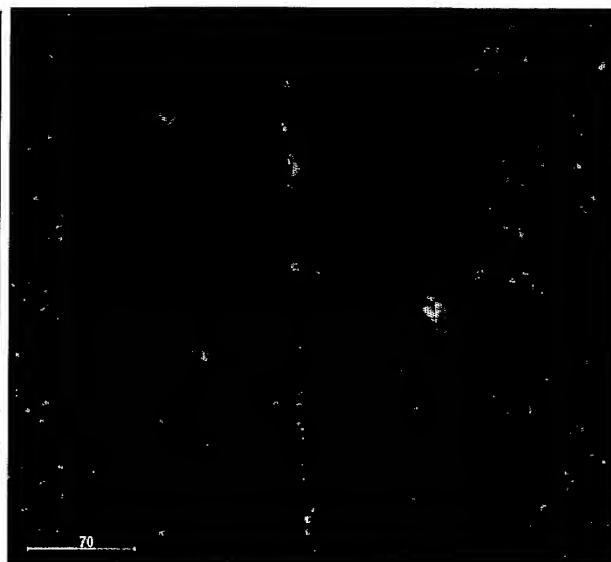


37/43
Fig. 12

A



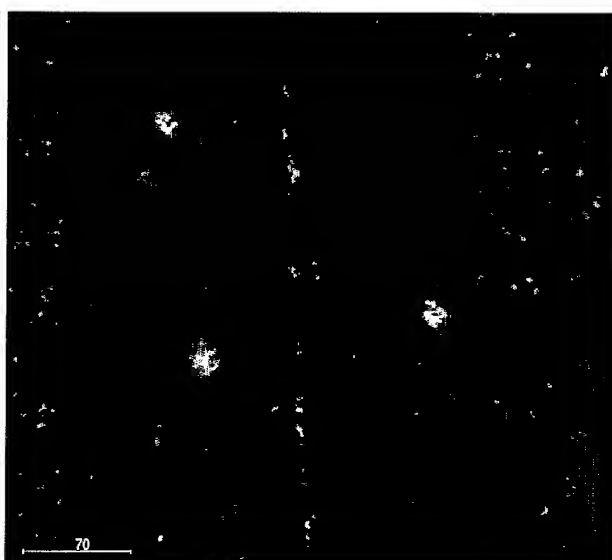
B



C

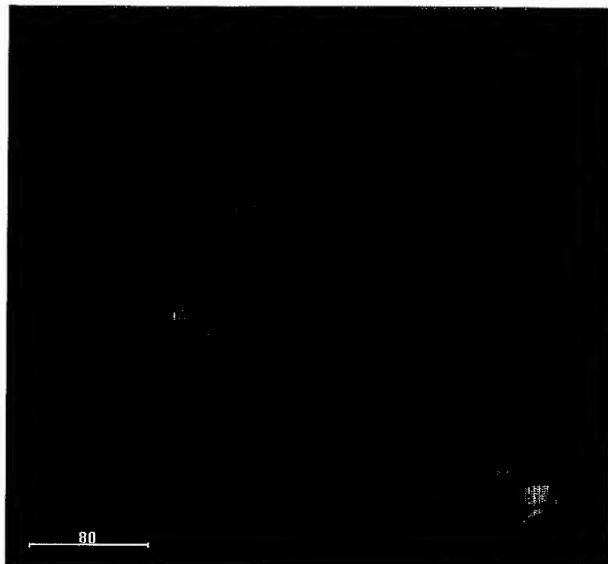


D

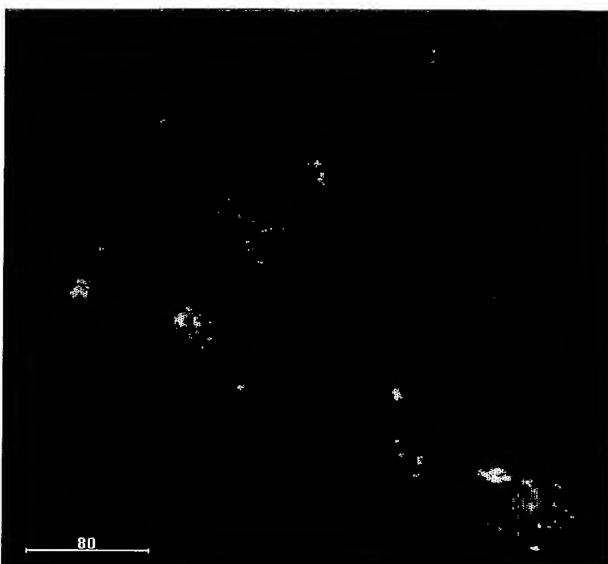


38/43 |
Fig. 13

A



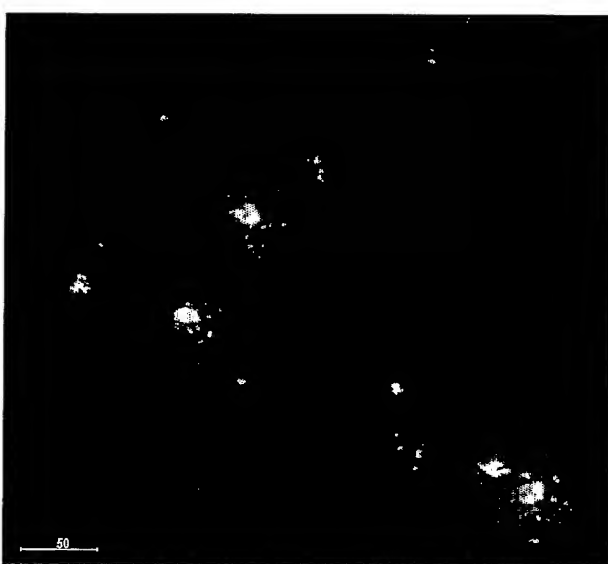
B



C



D

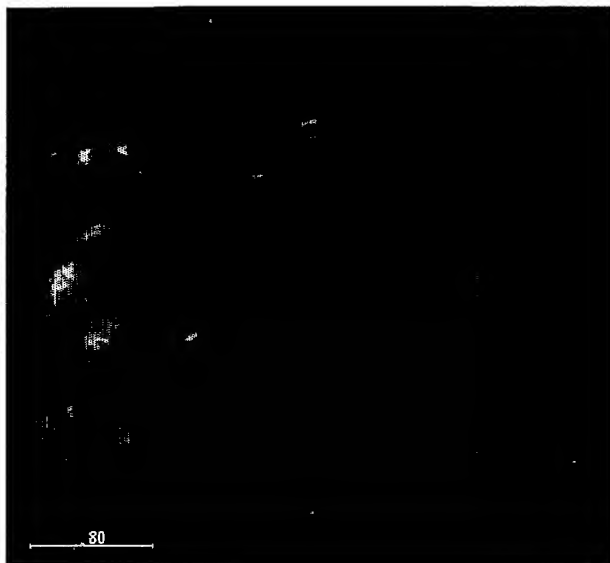


39/43
Fig. 14

A



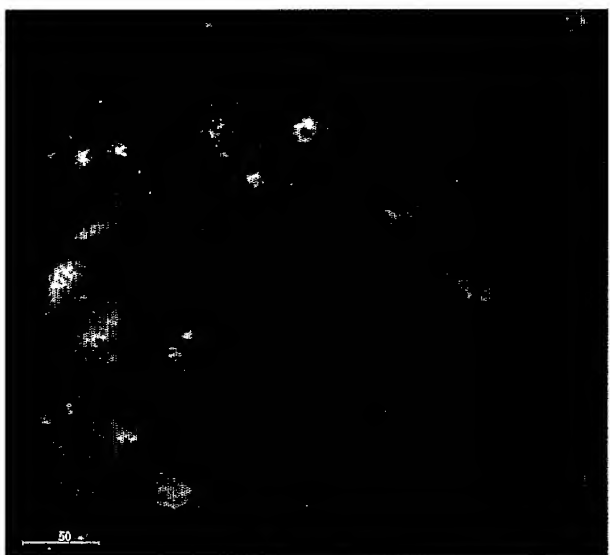
B



C

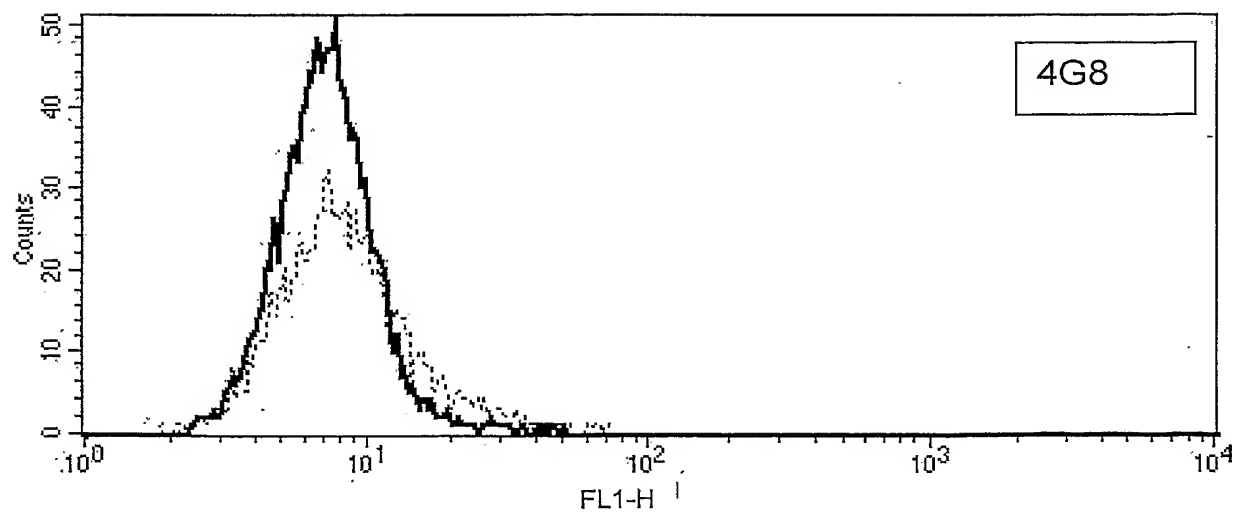
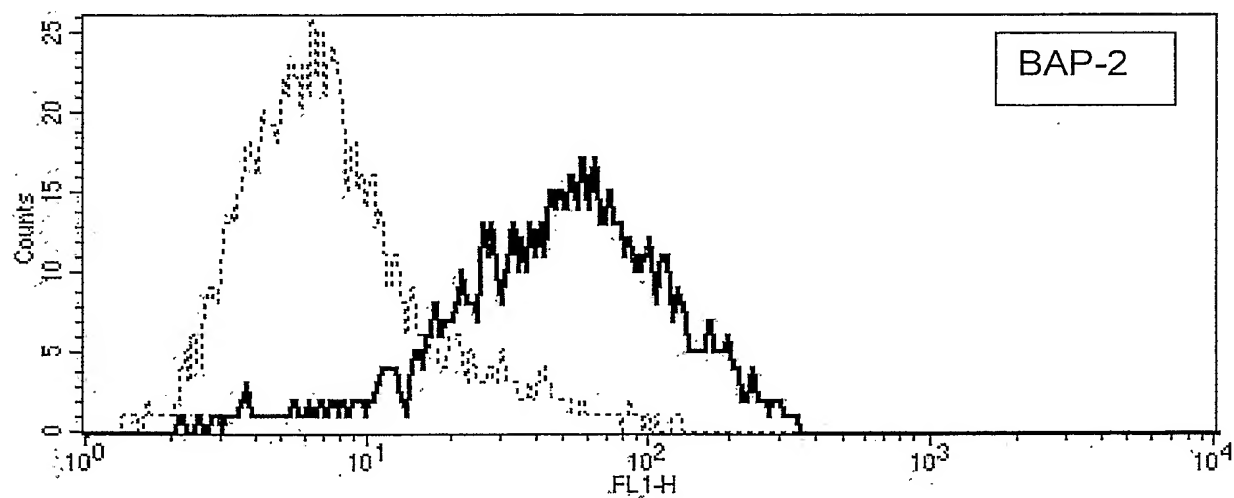
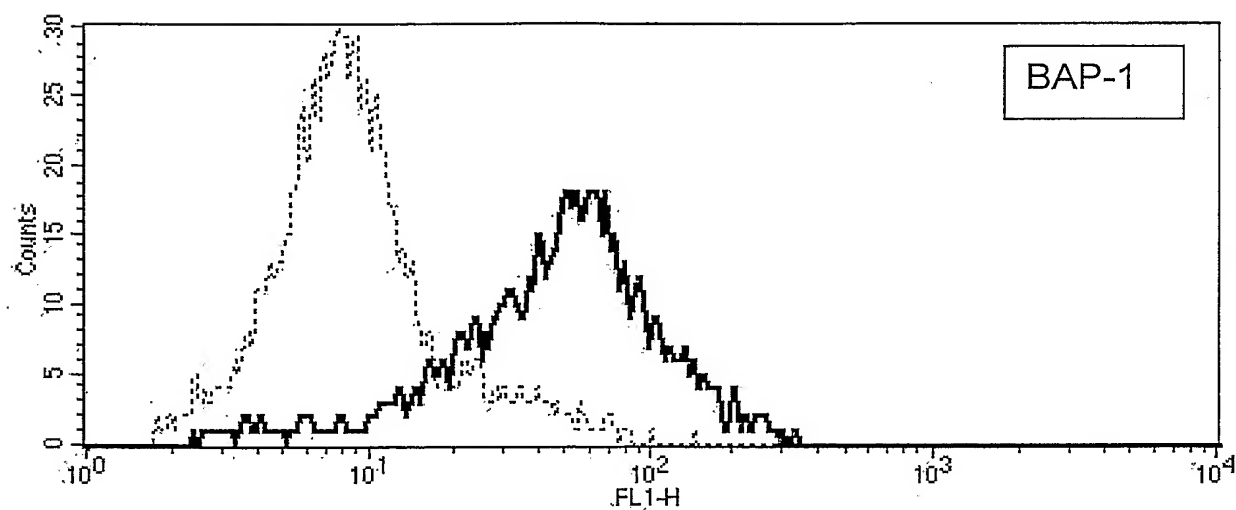


D



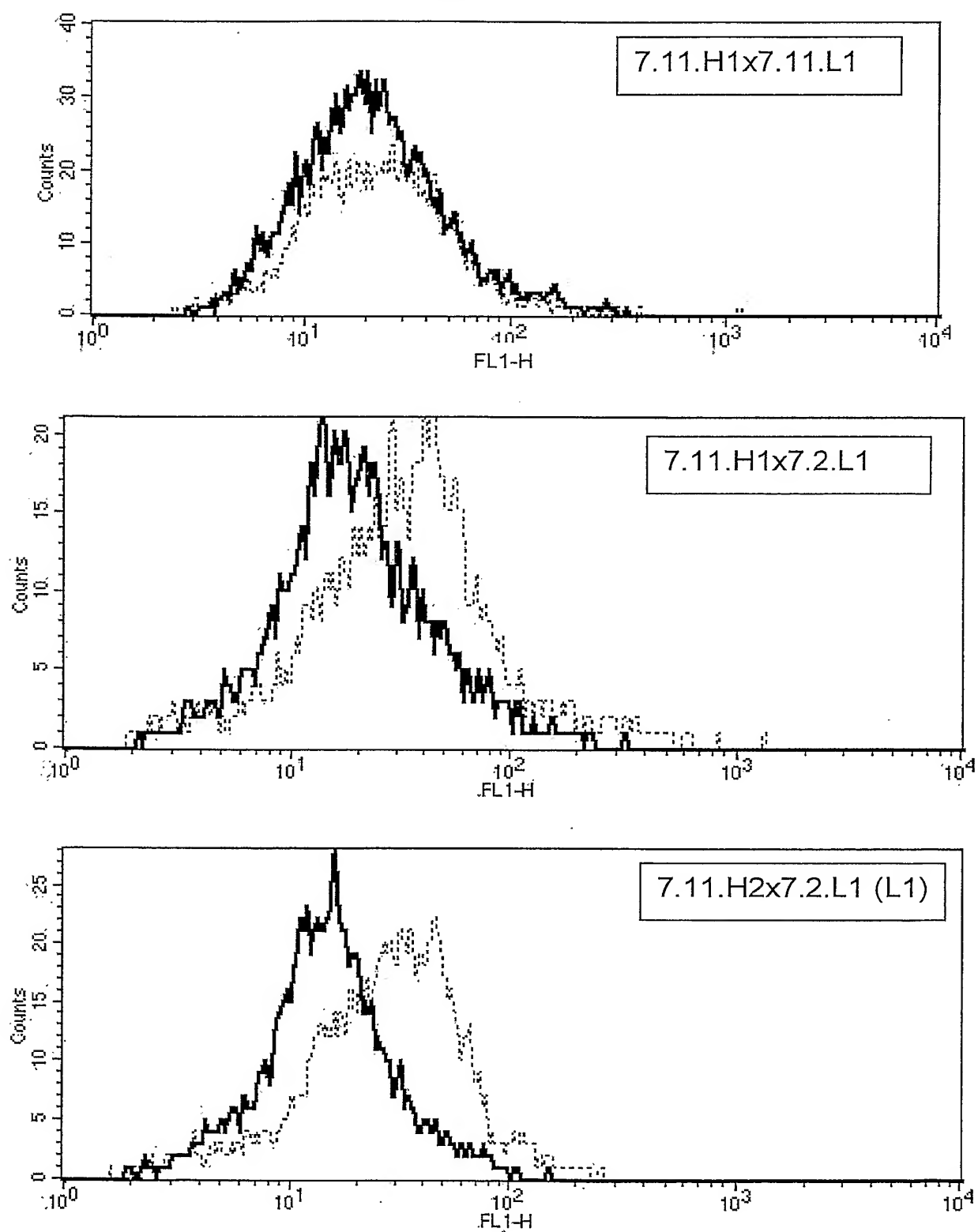
40/43

Fig. 15 - 1



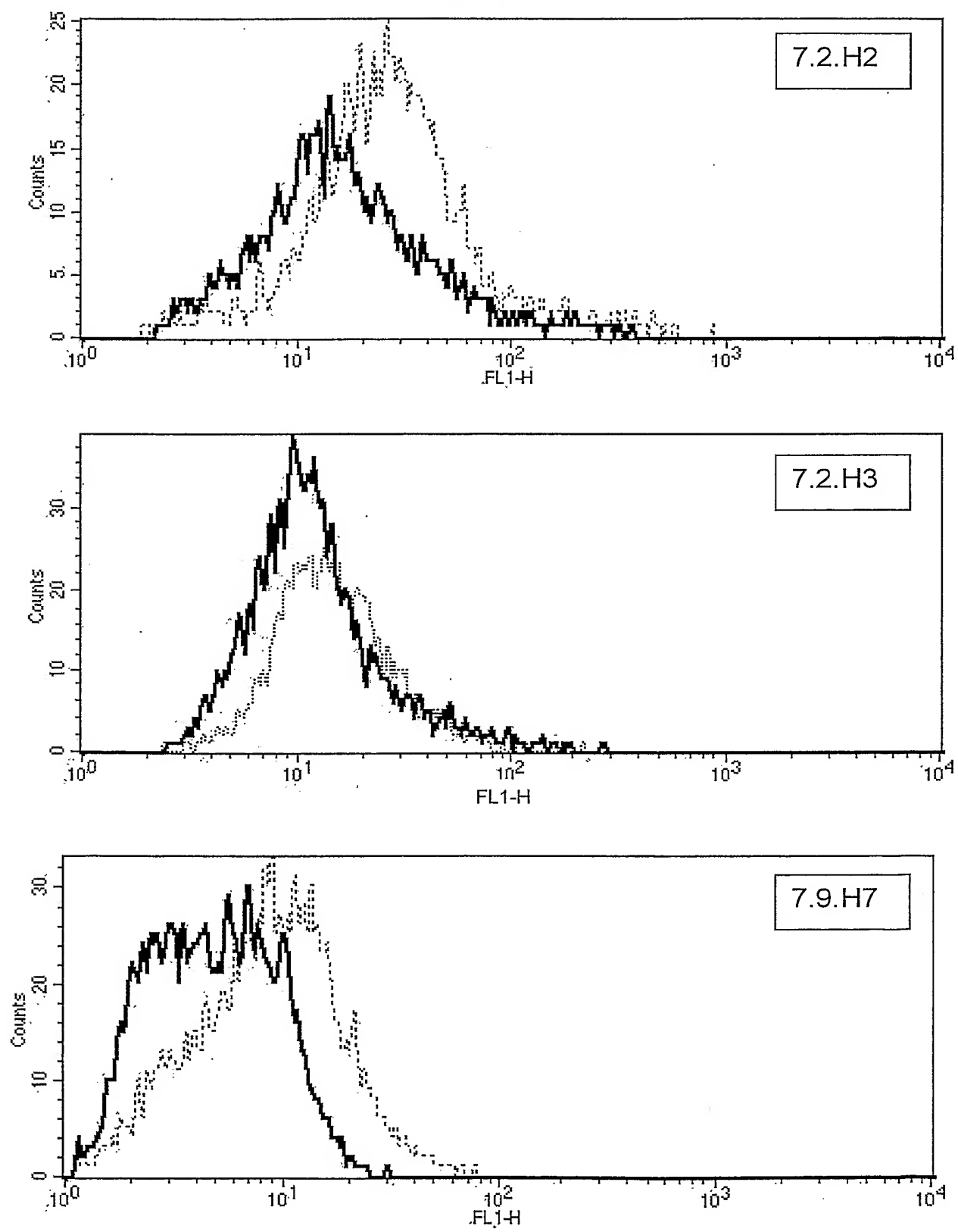
41/43

Fig. 15 - 2



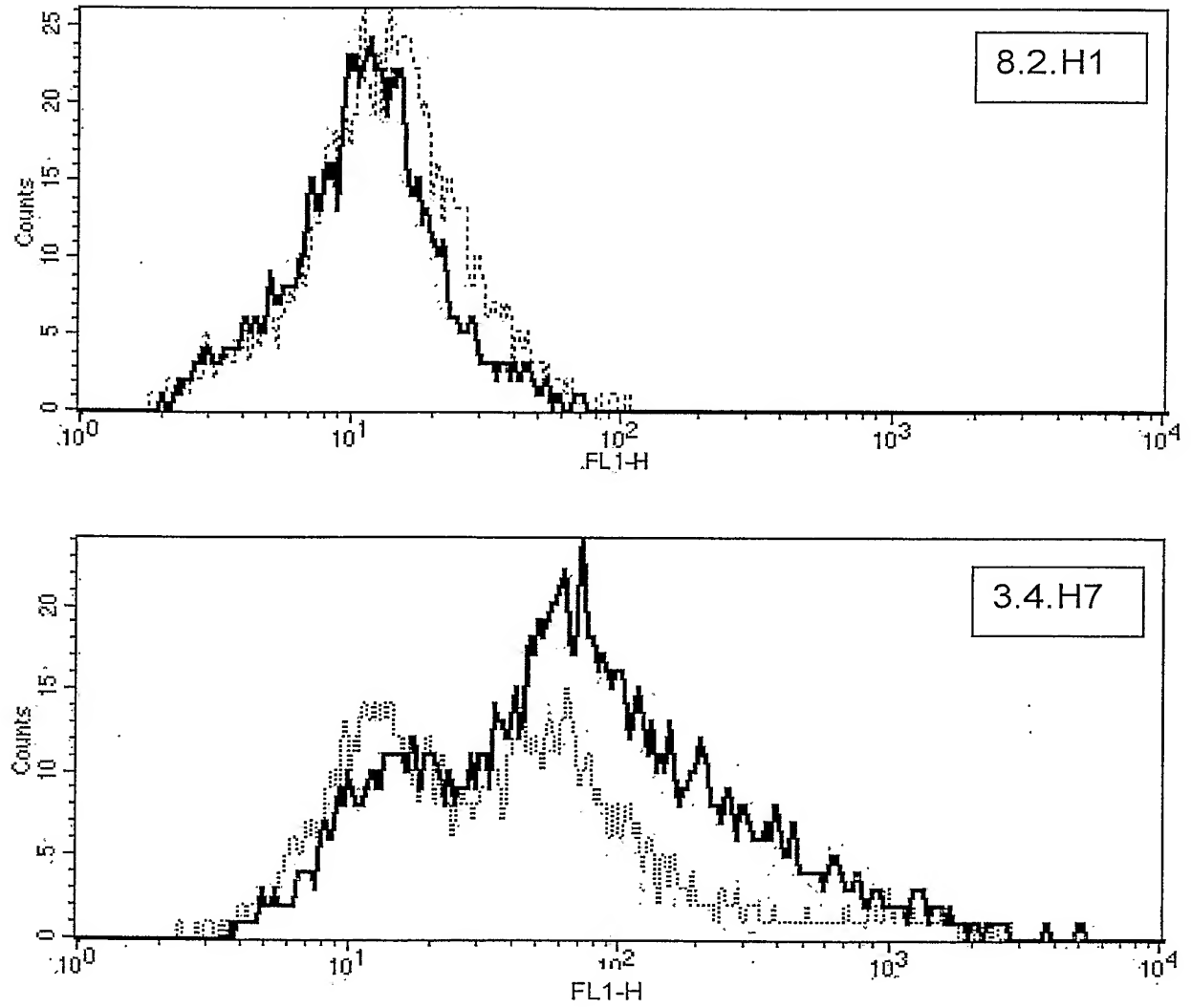
42/43

Fig. 15 - 3



43/43

Fig. 15 - 4



SEQUENCE LISTING

<110> F. Hoffmann-La Roche AG
MorphoSys AG

<120> Anti A-beta antibodies and their use

<130> F 2842 PCT

<140> EP 02003844.4

<141> 2002-02-20

<150> EP 02003844.4

<151> 2002-02-20

<160> 414

<170> PatentIn version 3.1

<210> 1

<211> 9

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; first region of beta-A4 peptide

<400> 1

Ala Glu Phe Arg His Asp Ser Gly Tyr
1 5

<210> 2

<211> 14

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; second region of beta-A4 peptide

<400> 2

Val His His Gln Lys Leu Val Phe Phe Ala Glu Asp Val Gly
1 5 10

<210> 3

<211> 368

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VH-region of MS-Roche#3

<400> 3

caggtgcaat tgggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccgatt taccttttagc agctatgcga tgagctgggt gcgccaagcc 120

2/165

```

cctgggaagg gtctcgagtg ggtgagcgcg attagcggta gcggcggcag cacctattat    180
gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat    240
ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtcttact    300
cattatgctc gttattatcg ttattttgat gtttggggcc aaggcaccct ggtgacggtt    360
agctcagc                                     368

```

```

<210> 4
<211> 122
<212> PRT
<213> artificial sequence

```

```

<220>
<223> synthetic construct; VH-region of MS-Roche#3

```

```

<400> 4

```

```

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1           5           10           15

```

```

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
          20           25           30

```

```

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
          35           40           45

```

```

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
          50           55           60

```

```

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65           70           75           80

```

```

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
          85           90           95

```

```

Ala Arg Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val Trp
          100          105          110

```

```

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
          115          120

```

```

<210> 5
<211> 379
<212> DNA
<213> artificial sequence

```

3/165

<220>

<223> synthetic construct; VH-region of MS-Roche#7

<400> 5

```

caggtgcaat tgggtgaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg      60
agctgcgcgg cctccggatt tacctttagc agctatgcga tgagctgggt gcgccaagcc      120
cctgggaagg gtctcgagtg ggtgagcgcg attagcggta gcggcggcag cacctattat      180
gcggatagcg tgaaaggccg ttaccattt cagctgataa ttcgaaaaac accctgtatc      240
tgcaaatgaa cagcctgcgt gcggaagata cggccgtgta ttattgcgcg cgtggtaagg      300
gtaataactca taagccttat ggttatgttc gttattttga tgtttggggc caaggcaccc      360
tggtgacggt tagctcagc                                     379

```

<210> 6

<211> 126

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VH-region of MS-Roche#7

<400> 6

```

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1           5           10           15

```

```

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
          20           25           30

```

```

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
          35           40           45

```

```

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
          50           55           60

```

```

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65           70           75           80

```

```

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
          85           90           95

```

```

Ala Arg Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr
          100          105          110

```

```

Phe Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
          115          120          125

```

4/165

<210> 7
 <211> 374
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VH-region of MS-Roche#8

<400> 7
 caggtgcaat tgggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60
 agctgcgcgg cctccggatt taccttttagc agctatgcga tgagctgggt gcgccaagcc 120
 cctgggaagg gtctcgagtg ggtgagcgcg attagcggta gcggcggcag cacctattat 180
 gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240
 ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtcttctt 300
 tctcgtgggtt ataatgggta ttatcataag tttgatgttt ggggcccaagg caccctgggtg 360
 acggttagct cagc 374

<210> 8
 <211> 124
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; VH-region of MS-Roche#8

<400> 8
 Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

5/165

Ala Arg Leu Leu Ser Arg Gly Tyr Asn Gly Tyr Tyr His Lys Phe Asp
100 105 110

Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

```
<210> 9
<211> 330
<212> DNA
<213> artificial sequence
```

<220>
<223> synthetic construct; VL-region of MS-Roche#3

[illegible]

```
<210> 10
<211> 110
<212> PRT
<213> artificial sequence
```

```
<220>
<223> synthetic construct; VL-region of MS-Roche#3
```

<400> 10

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80

6/165

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Val Tyr Asn Pro Pro
 85 90 95

Val Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
 100 105 110

<210> 11
 <211> 330
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VL-region of MS-Roche#7

<400> 11
 gatatcgtgc tgaccagag cccggcgacc ctgagcctgt ctccgggcca acgtgcgacc 60
 ctgagctgca gagcgagcca gagcgtgagc agcagctatc tggcgtggta ccagcagaaa 120
 ccaggtcaag caccgcgtct attaatattat ggcgcgagca gccgtgcaac tgggggtccc 180
 gcgcgtttta gcggtctctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240
 cctgaagact ttgcgactta ttattgcttt cagctttatt ctgatacttt tacctttggc 300
 cagggtacga aagttgaaat taaacgtacg 330

<210> 12
 <211> 110
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; VL-region of MS-Roche#7

<400> 12

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
 50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu

7/165

65 70 75 80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Leu Tyr Ser Asp Pro
 85 90 95

Phe	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg	Thr
			100					105					110

```
<210> 13
<211> 330
<212> DNA
<213> artificial sequence
```

```
<220>
<223> synthetic construct; VL-region of MS-Roche#8
```

<400>	13						
gatatcgtgc	tgacccagag	cccggcgacc	ctgagcctgt	ctccggggcga	acgtgcgacc	60	
ctgagctgca	gagcgagcca	gagcgtgagc	agcagctatc	tggcgtggta	ccagcagaaa	120	
ccagggtcaag	caccgcgtct	attaatttat	ggcgcgagca	gccgtgcaac	tgggggtcccg	180	
gcgcgttttta	gcggctctgg	atccggcacg	gattttaccc	tgaccattag	cagcctggaa	240	
cctgaagact	ttgcgactta	ttattgccag	cagctttctt	cttttctctc	tacctttggc	300	
cagggtacga	aagttgaaat	taaacgtacg				330	

```
<210> 14
<211> 110
<212> PRT
<213> artificial sequence
```

<220>
<223> synthetic construct; VL-region of MS-Roche#8

<400> 14

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60

8/165

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
 65 70 75 80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Ser Ser Phe Pro
 85 90 95

Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
 100 105 110

<210> 15
 <211> 24
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; CDR3 of VL-region of MS-Roche#3

<400> 15
 cagcaggttt ataatcctcc tggt 24

<210> 16
 <211> 8
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; CDR3 of VL-region of MS-Roche#3

<400> 16

Gln Gln Val Tyr Asn Pro Pro Val
 1 5

<210> 17
 <211> 24
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; CDR3 of VL-region of MS-Roche#7

<400> 17
 tttcagcttt attctgatcc tttt 24

<210> 18
 <211> 8
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; CDR3 of VL-region of MS-Roche#7

<400> 18

9/165

Phe Gln Leu Tyr Ser Asp Pro Phe
1 5

<210> 19
<211> 24
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct; CDR3 of VL-region of MS-Roche#8

<400> 19
cagcagcttt cttctttttcc tcct

24

<210> 20
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; CDR3 of VL-region of MS-Roche#8

<400> 20

Gln Gln Leu Ser Ser Phe Pro Pro
1 5

<210> 21
<211> 39
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct; CDR3 of VH-region of MS-Roche#3

<400> 21
cttactcatt atgctcggtta ttatcggttat tttgatggt

39

<210> 22
<211> 13
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; CDR3 of VH-region of MS-Roche#3

<400> 22

Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val
1 5 10

<210> 23
<211> 51

10/165

<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct; CDR3 of VH-region of MS-Roche#7

<400> 23
ggtaagggtataactcataa gccttatggt tatgttcggt attttgatgt t 51

<210> 24
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; CDR3 of VH-region of MS-Roche#7

<400> 24
Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
1 5 10 15

Val

<210> 25
<211> 45
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct; CDR3 of VH-region of MS-Roche#8

<400> 25
cttctttctc gtggttataa tgggtattat cataagtttg atggt 45

<210> 26
<211> 15
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; CDR3 of VH-region of MS-Roche#8

<400> 26
Leu Leu Ser Arg Gly Tyr Asn Gly Tyr Tyr His Lys Phe Asp Val
1 5 10 15

<210> 27
<211> 42
<212> PRT
<213> artificial sequence

11/165

<220>

<223> synthetic construct; beta-A4 peptide

<400> 27

Asp Ala Glu Phe Arg His Asp Ser Gly Tyr Glu Val His His Gln Lys
 1 5 10 15

Leu Val Phe Phe Ala Glu Asp Val Gly Ser Asn Lys Gly Ala Ile Ile
 20 25 30

Gly Leu Met Val Gly Gly Val Val Ile Ala
 35 40

<210> 28

<211> 17

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VL-primer for

<400> 28

gtggtggttc cgatatc

17

<210> 29

<211> 43

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VL-primer back

<400> 29

agcgtcacac tcggtgcggc tttcggctgg ccaagaacgg tta

43

<210> 30

<211> 17

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; control primer for

<400> 30

caggaaacag ctatgac

17

<210> 31

<211> 19

<212> DNA

<213> artificial sequence

<220>

12/165

<223> synthetic construct; control primer back

<400> 31

taccgttgct cttcacccc

19

<210> 32

<211> 360

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VH MS-Roche#3.6H5 x 3.6L2

<400> 32

caattggtgg aaagcggcgg cggcctggtg caaccgggcg gcagcctgcg tctgagctgc 60

gcggcctccg gatttacott tagcagctat gcgatgagct ggggtgcgcca agcccctggg 120

aagggtctcg agtgggtgag cgctattttct gagtctggta agactaagta ttatgctgat 180

tctgttaagg gtcgtttttac catttcacgt gataattcga aaaacaccct gtatctgcaa 240

atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtct tactcattat 300

gctcgttatt atcgttattt tgatgttttg ggccaaggca ccttggtgac ggtagctca 360

<210> 33

<211> 120

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VH MS-Roche#3.6H5 x 3.6L2

<400> 33

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
1 5 10 15Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
20 25 30Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala
35 40 45Ile Ser Glu Ser Gly Lys Thr Lys Tyr Tyr Ala Asp Ser Val Lys Gly
50 55 60Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
65 70 75 80

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg

13/165

85

90

95

Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val Trp Gly Gln
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 34
 <211> 360
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VH MS-Roche#3.6H8 x 3.6L2

<400> 34
 caattggtgg aaagcggcgg cggcctggtg caaccgggcg gcagcctgcg tctgagctgc 60
 gcggcctccg gatttacctt tagcagctat gcgatgagct ggggtgcgcca agcccctggg 120
 aagggtctcg agtgggtgag cgctatttct gagtattcta agtttaagta ttatgctgat 180
 tctgttaagg gtcgtttttac catttcacgt gataattcga aaaacaccct gtatctgcaa 240
 atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtct tactcattat 300
 gctcgttatt atcgttatatt tgatgtttgg ggccaaggca ccctggtgac ggtagctca 360

<210> 35
 <211> 120
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; VH MS-Roche#3.6H8 x 3.6L2

<400> 35

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
 1 5 10 15

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
 20 25 30

Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala
 35 40 45

Ile Ser Glu Tyr Ser Lys Phe Lys Tyr Tyr Ala Asp Ser Val Lys Gly
 50 55 60

14/165

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
65 70 75 80

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
85 90 95

Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 36
<211> 372
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct; VH MS-Roche#7.4H2 x 7.2L1

<400> 36
caattggtgg aaagcggcgg cggcctggtg caaccgggcg gcagcctgcg tctgagctgc 60
gcggcctccg gatttacctt tagcagctat gcgatgagct ggggtgcgcca agcccctggg 120
aagggtctcg agtgggtgag cgctattaat tataatggtg ctcgatattta ttatgctgat 180
tctgttaagg gtcgtttttac catttcacgt gataattcga aaaacaccct gtatctgcaa 240
atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtgg taagggtaat 300
actcataage cttatgggta tgttcgttat tttgatgttt ggggcccaagg caccctggtg 360
acggttagct ca 372

<210> 37
<211> 124
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; VH MS-Roche#7.4H2 x 7.2L1

<400> 37

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
1 5 10 15

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
20 25 30

Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala

15/165

35

40

45

Ile Asn Tyr Asn Gly Ala Arg Ile Tyr Tyr Ala Asp Ser Val Lys Gly
 50 55 60

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
 65 70 75 80

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
 85 90 95

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
 100 105 110

Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 38
 <211> 372
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VH MS-Roche#7.9H2 x 7.12L2

<400> 38
 caattggtgg aaagcggcgg cggcctggtg caaccgggcg gcagcctgcg tctgagctgc 60
 gcggcctccg gatttacctt tagcagctat gcgatgagct ggggtgcgcca agcccctggg 120
 aagggctctcg agtgggtgag cgctattaat gctgatggta atcgtaagta ttatgctgat 180
 tctgttaagg gtcgtttttac catttcacgt gataattcga aaaacaccct gtatctgcaa 240
 atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtgg taagggtaat 300
 actcataagc cttatgggta tggtcgttat tttgatgttt ggggcccaagg caccctggtg 360
 acggttagct ca 372

<210> 39
 <211> 124
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; VH MS-Roche#7.9H2 x 7.12L2

<400> 39

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
 1 5 10 15

16/165

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
20 25 30

Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala
35 40 45

Ile Asn Ala Asp Gly Asn Arg Lys Tyr Tyr Ala Asp Ser Val Lys Gly
50 55 60

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
65 70 75 80

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
85 90 95

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
100 105 110

Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 40
<211> 372
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct; VH MS-Roche#7.9H4 x 7.12L2

<400> 40
caattggtgg aaagcggcgg cggcctggtg caaccgggcg gcagcctgcg tctgagctgc 60
gcggcctccg gatttacott tagcagctat gcgatgagct ggggtgcgcca agcccctggg 120
aagggtctcg agtgggtgag cgctattaat gctgttggtg tgaagaagtt ttatgctgat 180
tctgttaagg gtcgtttttac catttcacgt gataattcga aaaacaccct gtatctgcaa 240
atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtgg taagggtaat 300
actcataagc cttatgggta tgttcgttat tttgatgttt ggggcccaagg caccctggtg 360
acggttagct ca 372

<210> 41
<211> 124
<212> PRT
<213> artificial sequence

17/165

<220>

<223> synthetic construct; VH MS-Roche#7.9H4 x 7.12L2

<400> 41

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
 1 5 10 15

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
 20 25 30

Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala
 35 40 45

Ile Asn Ala Val Gly Met Lys Lys Phe Tyr Ala Asp Ser Val Lys Gly
 50 55 60

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
 65 70 75 80

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
 85 90 95

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
 100 105 110

Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 42

<211> 372

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VH MS-Roche#7.11H1 x 7.11L1

<400> 42

caattggtgg aaagcggcgg cggcctggtg caaccgggcg gcagcctgcg tctgagctgc 60

gcggcctccg gatttacctt tagcagctat gcgatgagct gggcgcgcca agcccctggg 120

aagggtctcg agtgggtgag cgggtattaat gctgctgggtt ttcgtactta ttatgctgat 180

tctgttaagg gtcgttttac catttcacgt gataattcga aaaacaccct gtatctgcaa 240

atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtgg taagggtaat 300

actcataagc cttatgggta tggttcgttat tttgatgttt ggggccaagg caccctgggtg 360

acggtttagct ca 372

18/165

<210> 43
 <211> 124
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; VH MS-Roche#7.11H1 x 7.11L1

<400> 43

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
 1 5 10 15

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
 20 25 30

Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Gly
 35 40 45

Ile Asn Ala Ala Gly Phe Arg Thr Tyr Tyr Ala Asp Ser Val Lys Gly
 50 55 60

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
 65 70 75 80

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
 85 90 95

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
 100 105 110

Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 44
 <211> 372
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VH MS-Roche#7.11H1 x 7.2L1

<400> 44
 caattggtgg aaagcggcgg cggcctggtg caaccgggcg gcagcctgcg tctgagctgc 60
 gcggcctccg gatttacctt tagcagctat gcgatgagct gggcgcgcca agcccctggg 120
 aagggctctcg agtgggtgag cgggtattaat gctgctgggtt ttctgtactta ttatgctgat 180

19/165

tctgttaagg gtcgtttttac catttcacgt gataattcga aaaacaccct gtatctgcaa 240
 atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtgg taagggtaat 300
 actcataagc cttatgggta tgttcgttat tttgatgttt ggggcccaagg caccctgggtg 360
 acggtttagct ca 372

<210> 45
 <211> 124
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; VH MS-Roche#7.11H1 x 7.2L1

<400> 45

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
 1 5 10 15

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
 20 25 30

Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Gly
 35 40 45

Ile Asn Ala Ala Gly Phe Arg Thr Tyr Tyr Ala Asp Ser Val Lys Gly
 50 55 60

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
 65 70 75 80

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
 85 90 95

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
 100 105 110

Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 46
 <211> 330
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VL MS-Roche#3.6H5 x 3.6L2

20/165

<400> 46
 gatatcgtgc tgaccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc 60
 ctgagctgca gagcgagcca gtttctttct cgttattatc tggcgtggta ccagcagaaa 120
 ccagggtcaag caccgcgtct attaatattat ggcgcgagca gccgtgcaac tgggggtcccg 180
 gcgcgtttta gcggtctctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240
 cctgaagact ttgcggttta ttattgccag cagacttata attatcctcc tacctttggc 300
 cagggtacga aagttgaaat taaacgtacg 330

<210> 47
 <211> 110
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; VL MS-Roche#3.6H5 x 3.6L2

<400> 47

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Phe Leu Ser Arg Tyr
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
 50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
 65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Thr Tyr Asn Tyr Pro
 85 90 95

Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
 100 105 110

<210> 48
 <211> 330
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VL MS-Roche#3.6H8 x 3.6L2

21/165

```

<400> 48
gatatcgtgc tgaccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc      60
ctgagctgca gagcgagcca gtttctttct cgttattatc tggcgtggta ccagcagaaa      120
ccagggtcaag caccgctctt attaatattat ggcgcgagca gccgtgcaac tgggggtcccg      180
gcgcggtttta gcggctcttg atccggcaacg gattttaccc tgaccattag cagcctggaa      240
cctgaagact ttgcggttta ttattgccag cagacttata attatcctcc tacctttggc      300
cagggtacga aagttgaaat taaacgtacg                                     330

```

```

<210> 49
<211> 110
<212> PRT
<213> artificial sequence

```

```

<220>
<223> synthetic construct; VL MS-Roche#3.6H8 x 3.6L2

```

```

<400> 49

```

```

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1           5           10           15

```

```

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Phe Leu Ser Arg Tyr
          20           25           30

```

```

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
          35           40           45

```

```

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
          50           55           60

```

```

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65           70           75           80

```

```

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Thr Tyr Asn Tyr Pro
          85           90           95

```

```

Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
          100          105          110

```

```

<210> 50
<211> 330
<212> DNA
<213> artificial sequence

```

```

<220>

```

22/165

<223> synthetic construct; VL MS-Roche#7.4H2 x 7.2L1

<400> 50

gatatcgtgc tgacccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc 60

ctgagctgca gagcgagcca gtatgttgat cgtacttatc tggcgtggta ccagcagaaa 120

ccaggtcaag caccgctctc attaatattat ggcgcgagca gccgtgcaac tgggggtccc 180

gcgcgtttta gcggctctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240

cctgaagact ttgcgactta ttattgccag cagatttatt cttttcctca tacctttggc 300

cagggtacga aagttgaaat taaacgtacg 330

<210> 51

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL MS-Roche#7.4H2 x 7.2L1

<400> 51

Asp	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser	Leu	Ser	Pro	Gly
1				5					10					15	

Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala	Ser	Gln	Tyr	Val	Asp	Arg	Thr
			20					25					30		

Tyr	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Leu	Leu
		35					40					45			

Ile	Tyr	Gly	Ala	Ser	Ser	Arg	Ala	Thr	Gly	Val	Pro	Ala	Arg	Phe	Ser
	50					55				60					

Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Glu
65					70					75					80

Pro	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ile	Tyr	Ser	Phe	Pro
			85						90					95	

His	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg	Thr
			100					105					110

<210> 52

<211> 330

<212> DNA

<213> artificial sequence

23/165

<220>

<223> synthetic construct; VL MS-Roche#7.9H2 x 7.12L2

<400> 52

```
gatatcgtgc tgaccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc      60
ctgagctgca gagcgagcca gcgttttttt tataagtatc tggcgtggta ccagcagaaa      120
ccaggtcaag caccgctctc attaatctct ggttcttcta accgtgcaac tgggggtcccg      180
gcgcgtttta gcggctctgg atccggcacg gatctttacc tgaccattag cagcctggaa      240
cctgaagact ttgcggttta ttattgcctt cagctttata atattcctaa tacctttggc      300
caggggtacga aagttgaaat taaacgtacg                                     330
```

<210> 53

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL MS-Roche#7.9H2 x 7.12L2

<400> 53

```
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1           5           10          15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Phe Phe Tyr Lys
          20          25          30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
          35          40          45

Ile Ser Gly Ser Ser Asn Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
          50          55          60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65          70          75          80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Leu Tyr Asn Ile Pro
          85          90          95

Asn Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
          100         105         110
```

<210> 54

<211> 330

<212> DNA

<213> artificial sequence

24/165

<220>

<223> synthetic construct; VL MS-Roche#7.9H4 x 7.12L2

<400> 54

```

gatatcgtgc tgaccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc      60
ctgagctgca gagcgagcca gcgttttttt tataagtatc tggcgtggta ccagcagaaa      120
ccaggtcaag caccgctctt attaatctct ggttcttcta accgtgcaac tgggggtccc      180
gcgcgtttta gcggctctgg atccggcacg gattttaccc tgaccattag cagcctggaa      240
cctgaagact ttgcggttta ttattgcctt cagctttata atattcctaa tacctttggc      300
caggttacga aagttgaaat taaacgtacg                                     330

```

<210> 55

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL MS-Roche#7.9H4 x 7.12L2

<400> 55

```

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1           5           10           15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Phe Phe Tyr Lys
          20           25           30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
          35           40           45

Ile Ser Gly Ser Ser Asn Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
          50           55           60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65           70           75           80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Leu Tyr Asn Ile Pro
          85           90           95

Asn Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
          100          105          110

```

<210> 56

<211> 330

<212> DNA

25/165

<213> artificial sequence

<220>

<223> synthetic construct; VL MS-Roche#7.11H1 x 7.11L1

<400> 56

gatatcgtgc tgacccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc 60
ctgagctgca gagcgagcca gcgtattctt cgtatttatc tggcgtggta ccagcagaaa 120
ccagggtcaag caccgcgtct attaatattat ggcgcgagca gccgtgcaac tgggggtcccg 180
gcgcgtttta gcggctctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240
cctgaagact ttgcgactta ttattgccag caggtttatt ctctctctca tacctttggc 300
cagggtacga aagttgaaat taaacgtacg 330

<210> 57

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL MS-Roche#7.11H1 x 7.11L1

<400> 57

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Ile Leu Arg Ile
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Val Tyr Ser Pro Pro
85 90 95
His Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 58

<211> 330

26/165

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VL MS-Roche#7.11H1 x 7.2L1

<400> 58

```

gatatcgtgc tgaccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc      60
ctgagctgca gagcgagcca gtatgttgat cgtacttatac tggcgtggta ccagcagaaa    120
ccagggtcaag caccgcgtct attaatattat ggcgcgagca gccgtgcaac tgggggtcccg    180
gcgcgtttta gcggctctgg atccggcacg gattttaccc tgaccattag cagcctggaa    240
cctgaagact ttgcgactta ttattgccag cagatattatt cttttcctca tacctttggc    300
cagggtacga aagttgaaat taaacgtacg                                     330

```

<210> 59

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL MS-Roche#7.11H1 x 7.2L1

<400> 59

```

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1           5           10           15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Tyr Val Asp Arg Thr
          20           25           30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
          35           40           45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
          50           55           60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65           70           75           80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ile Tyr Ser Phe Pro
          85           90           95

His Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
          100          105          110

```

<210> 60

27/165

<211> 39
<212> DNA
<213> artificial sequence

<220>
<223> HCDR3 MS-Roche#3.6H5 x 3.6L2

<400> 60
cttactcatt atgctcgta ttatcgttat tttgatgtt 39

<210> 61
<211> 13
<212> PRT
<213> artificial sequence

<220>
<223> HCDR3 MS-Roche#3.6H5 x 3.6L2

<400> 61

Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val
1 5 10

<210> 62
<211> 39
<212> DNA
<213> artificial sequence

<220>
<223> HCDR3 MS-Roche#3.6H8 x 3.6L2

<400> 62
cttactcatt atgctcgta ttatcgttat tttgatgtt 39

<210> 63
<211> 13
<212> PRT
<213> artificial sequence

<220>
<223> HCDR3 MS-Roche#3.6H8 x 3.6L2

<400> 63

Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val
1 5 10

<210> 64
<211> 51
<212> DNA
<213> artificial sequence

<220>
<223> HCDR3 MS-Roche#7.4H2x7.2L1

28/165

<400> 64
ggtaagggtataactcataa gccttatgggtatgttcggtatgttgatgt t 51

<210> 65
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> HCDR3 MS-Roche#7.4H2x7.2L1

<400> 65
Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
1 5 10 15

Val

<210> 66
<211> 51
<212> DNA
<213> artificial sequence

<220>
<223> HCDR3 MS-Roche#7.9H2x7.12L2

<400> 66
ggtaagggtataactcataa gccttatgggtatgttcggtatgttgatgt t 51

<210> 67
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> HCDR3 MS-Roche#7.9H2x7.12L2

<400> 67
Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
1 5 10 15

Val

<210> 68
<211> 51
<212> DNA
<213> artificial sequence

<220>
<223> HCDR3 MS-Roche#7.9H4x7.12L2

29/165

<400> 68
ggtaagggtataactcataa gccttatgggt tatgttcggtt attttgatgt t 51

<210> 69
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> HCDR3 MS-Roche#7.9H4x7.12L2

<400> 69
Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
1 5 10 15

Val

<210> 70
<211> 51
<212> DNA
<213> artificial sequence

<220>
<223> HCDR3 MS-Roche#7.11H1x7.11L1

<400> 70
ggtaagggtataactcataa gccttatgggt tatgttcggtt attttgatgt t 51

<210> 71
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> HCDR3 MS-Roche#7.11H1x7.11L1

<400> 71
Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
1 5 10 15

Val

<210> 72
<211> 51
<212> DNA
<213> artificial sequence

<220>

30/165

<223> HCDR3 MS-Roche#7.11H1x7.2L1

<400> 72

ggtaagggtataactcataa gccttatggt tatgttcgtt atttgatgt t

51

<210> 73

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> HCDR3 MS-Roche#7.11H1x7.2L1

<400> 73

Gly	Lys	Gly	Asn	Thr	His	Lys	Pro	Tyr	Gly	Tyr	Val	Arg	Tyr	Phe	Asp
1				5					10					15	

Val

<210> 74

<211> 24

<212> DNA

<213> artificial sequence

<220>

<223> LCDR3 MS-Roche#3.6H5 x 3.6L2

<400> 74

cagcagactt ataattatcc tcct

24

<210> 75

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> LCDR3 MS-Roche#3.6H5 x 3.6L2

<400> 75

Gln	Gln	Thr	Tyr	Asn	Tyr	Pro	Pro
1				5			

<210> 76

<211> 24

<212> DNA

<213> artificial sequence

<220>

<223> LCDR3 MS-Roche#3.6H8 x 3.6L2

<400> 76

31/165

cagcagactt ataattatcc tcct

24

<210> 77

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> LCDR3 MS-Roche#3.6H8 x 3.6L2

<400> 77

Gln Gln Thr Tyr Asn Tyr Pro Pro
1 5

<210> 78

<211> 24

<212> DNA

<213> artificial sequence

<220>

<223> LCDR3 MS-Roche#7.4H2x7.2L1

<400> 78

cagcagattt attcttttcc tcat

24

<210> 79

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> LCDR3 MS-Roche#7.4H2x7.2L1

<400> 79

Gln Gln Ile Tyr Ser Phe Pro His
1 5

<210> 80

<211> 24

<212> DNA

<213> artificial sequence

<220>

<223> LCDR3 MS-Roche#7.9H2x7.12L2

<400> 80

cttcagcttt ataattatcc taat

24

<210> 81

<211> 8

<212> PRT

<213> artificial sequence

32/165

<220>
<223> LCDR3 MS-Roche#7.9H2x7.12L2
<400> 81

Leu Gln Leu Tyr Asn Ile Pro Asn
1 5

<210> 82
<211> 24
<212> DNA
<213> artificial sequence

<220>
<223> LCDR3 MS-Roche#7.9H4x7.12L2

<400> 82
cttcagcttt ataatatcc taat

24

<210> 83
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> LCDR3 MS-Roche#7.9H4x7.12L2

<400> 83

Leu Gln Leu Tyr Asn Ile Pro Asn
1 5

<210> 84
<211> 24
<212> DNA
<213> artificial sequence

<220>
<223> LCDR3 MS-Roche#7.11H1x7.11L1

<400> 84
cagcaggttt attctcctcc tcat

24

<210> 85
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> LCDR3 MS-Roche#7.11H1x7.11L1

<400> 85

Gln Gln Val Tyr Ser Pro Pro His

33/165

1

5

<210> 86
<211> 24
<212> DNA
<213> artificial sequence

<220>
<223> LCDR3 MS-Roche#7.11H1x7.2L1

<400> 86
cagcagattt attctttttcc tcat

24

<210> 87
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> LCDR3 MS-Roche#7.11H1x7.2L1

<400> 87

Gln Gln Ile Tyr Ser Phe Pro His
1 5

<210> 88
<211> 378
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct; VH MS-Roche#7.9H7

<400> 88
caggtgcaat tgggtggaaag cgggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60
agctgcgcgg cctccggatt tacctttagc agctatgcga tgagctgggt gcgccaagcc 120
cctgggaagg gtctcgagtg ggtgagcgct attaatgctt ctggtactcg tacttattat 180
gctgattctg ttaagggtcg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240
ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtggtaag 300
ggtaatactc ataagcctta tggttatgtt cgttattttg atgtttgggg ccaaggcacc 360
ctggtgacgg ttagctca 378

<210> 89
<211> 126
<212> PRT
<213> artificial sequence

<220>

34/165

<223> synthetic construct; VH MS-Roche#7.9H7

<400> 89

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Asn Ala Ser Gly Thr Arg Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr
 100 105 110

Phe Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 90

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VL MS-Roche#7.9H7

<400> 90

gatatcgtgc tgaccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc 60
 ctgagctgca gagcgagcca gagcgtgagc agcagctatc tggcgtggta ccagcagaaa 120
 ccaggtaag caccgcgtct attaatat ggcgcgagca gccgtgcaac tgggggtccc 180
 ggcggtttta ggcgctctgg atccggcacg gattttacc tgaccattag cagcctggaa 240
 cctgaagact ttgcgactta ttattgcctt cagatttata atatgcctat tacctttggc 300
 cagggtacga aagttgaaat taaacgtacg 330

<210> 91

35/165

<211> 110
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; VL MS-Roche#7.9H7

<400> 91

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
 50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
 65 70 75 80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Ile Tyr Asn Met Pro
 85 90 95

Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
 100 105 110

<210> 92
 <211> 51
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; HCDR3 MS-Roche#7.9H7

<400> 92
 ggtaagggtataactcataa gccttatgggt tatgttcggtt attttgatgt t 51

<210> 93
 <211> 17
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; HCDR3 MS-Roche#7.9H7

<400> 93

36/165

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
1 5 10 15

Val

<210> 94
<211> 24
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 MS-Roche#7.9H7

<400> 94
cttcagattt ataatatgcc tatt

24

<210> 95
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 MS-Roche#7.9H7

<400> 95

Leu Gln Ile Tyr Asn Met Pro Ile
1 5

<210> 96
<211> 12
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR1 of MS-Roche#3

<400> 96

Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala
1 5 10

<210> 97
<211> 7
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR2 of MS-Roche#3

<400> 97

Gly Ala Ser Ser Arg Ala Thr

37/165

1

5

<210> 98
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#3
<400> 98

Gln Gln Val Tyr Asn Pro Pro Val
1 5

<210> 99
<211> 10
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR1 of MS-Roche#3
<400> 99

Gly Phe Thr Phe Ser Ser Tyr Ala Met Ser
1 5 10

<210> 100
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3
<400> 100

Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 101
<211> 13
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR3 of MS-Roche#3
<400> 101

38/165

Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val
1 5 10

<210> 102
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#3.1

<400> 102

Gln Gln Val Tyr Ser Val Pro Pro
1 5

<210> 103
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#3.2

<400> 103

Gln Gln Ile Tyr Ser Tyr Pro Pro
1 5

<210> 104
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#3.3

<400> 104

His Gln Met Ser Ser Tyr Pro Pro
1 5

<210> 105
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#3.4

<400> 105

Gln Gln Thr Tyr Asp Tyr Pro Pro
1 5

39/165

<210> 106
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#3.5

<400> 106

Gln Gln Ile Tyr Asp Tyr Pro Pro
1 5

<210> 107
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#3.6

<400> 107

Gln Gln Thr Tyr Asn Tyr Pro Pro
1 5

<210> 108
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3.2H1

<400> 108

Ala Ile Ser Glu His Gly Leu Asn Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 109
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3.2H2

<400> 109

Ala Ile Ser Gln Arg Gly Gln Phe Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

40/165

Gly

<210> 110
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3.3H1

<400> 110

Val	Ile	Ser	Glu	Lys	Ser	Arg	Phe	Ile	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 111
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3.3H2

<400> 111

Val	Ile	Ser	Gln	Glu	Ser	Gln	Tyr	Lys	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 112
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3.3H3

<400> 112

Ala	Ile	Ser	Gln	Asn	Gly	Phe	His	Ile	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

41/165

<210> 113
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3.4H1

<400> 113

Ala	Ile	Ser	Glu	Thr	Ser	Ile	Arg	Lys	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 114
<211> 16
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3.4H2

<400> 114

Val	Ile	Asp	Met	Val	Gly	His	Thr	Tyr	Tyr	Ala	Asp	Ser	Val	Lys	Gly
1				5					10					15	

<210> 115
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3.4H3

<400> 115

Val	Ile	Ser	Gln	Thr	Gly	Arg	Lys	Ile	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 116
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3.4H4

42/165

<400> 116

Ala	Ile	Ser	Glu	Thr	Gly	Met	His	Ile	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 117

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.4H5

<400> 117

Val	Ile	Ser	Gln	Val	Gly	Ala	His	Ile	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 118

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.4H6

<400> 118

Ala	Ile	Ser	Glu	Ser	Gly	Trp	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 119

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.4H7

<400> 119

Val	Ile	Ser	Glu	Thr	Gly	Lys	Asn	Ile	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

43/165

Gly

<210> 120
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3.4H8

<400> 120

Ala	Ile	Ser	Glu	His	Gly	Arg	Phe	Lys	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5				10						15	

Gly

<210> 121
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3.4H9

<400> 121

Ala	Ile	Ser	Glu	Ser	Ser	Lys	Asn	Lys	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5				10						15	

Gly

<210> 122
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3.4H10

<400> 122

Ala	Ile	Ser	Glu	Ser	Gly	Arg	Gly	Lys	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5				10						15	

Gly

44/165

<210> 123
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3.4H11
<400> 123

Ala	Ile	Ser	Glu	Phe	Gly	Lys	Asn	Ile	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 124
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3.4H12
<400> 124

Val	Ile	Ser	Gln	Thr	Gly	Gln	Asn	Ile	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 125
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3.4H13
<400> 125

Ala	Ile	Ser	Glu	Gln	Gly	Arg	Asn	Ile	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 126
<211> 17
<212> PRT
<213> artificial sequence

45/165

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.4H14

<400> 126

Ala	Ile	Ser	Glu	Ser	Gly	Gln	Tyr	Lys	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 127

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.4H16

<400> 127

Ala	Ile	Ser	Glu	Ser	Gly	Val	Asn	Ile	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 128

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.4H17

<400> 128

Ala	Ile	Ser	Glu	Phe	Gly	Gln	Phe	Ile	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 129

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.4H18

<400> 129

46/165

Ala Ile Ser Gln Gln Ser Asn Phe Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 130
<211> 12
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR1 of MS-Roche#3.4L7
<400> 130

Arg Ala Ser Gln Arg Leu Gly Arg Leu Tyr Leu Ala
1 5 10

<210> 131
<211> 12
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR1 of MS-Roche#3.4L8
<400> 131

Arg Ala Ser Gln Trp Ile Thr Lys Ser Tyr Leu Ala
1 5 10

<210> 132
<211> 12
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR1 of MS-Roche#3.4L9
<400> 132

Arg Ala Ser Arg Arg Ile His Val Tyr Tyr Leu Ala
1 5 10

<210> 133
<211> 12
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR1 of MS-Roche#3.4L11
<400> 133

47/165

Arg Ala Ser Gln Leu Val Gly Arg Ala Tyr Leu Ala
1 5 10

<210> 134
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3.6H1

<400> 134

Val Ile Ser Glu Ser Gly Gln Tyr Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 135
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3.6H2

<400> 135

Val Ile Ser Glu Arg Gly Ile Asn Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 136
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3.6H3

<400> 136

Val Ile Ser Glu Thr Gly Lys Phe Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

48/165

<210> 137
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3.6H4
<400> 137

Ala	Ile	Ser	Glu	Arg	Gly	Arg	His	Ile	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 138
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3.6H5
<400> 138

Ala	Ile	Ser	Glu	Ser	Gly	Lys	Thr	Lys	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 139
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3.6H6
<400> 139

Ala	Ile	Ser	Glu	His	Gly	Thr	Asn	Ile	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 140
<211> 17
<212> PRT
<213> artificial sequence

49/165

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.6H8

<400> 140

Ala	Ile	Ser	Glu	Tyr	Ser	Lys	Phe	Lys	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 141

<211> 12

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR1 of MS-Roche#3.6L1

<400> 141

Arg	Ala	Ser	Gln	Phe	Ile	Gln	Arg	Phe	Tyr	Leu	Ala
1				5					10		

<210> 142

<211> 12

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR1 of MS-Roche#3.6L2

<400> 142

Arg	Ala	Ser	Gln	Phe	Leu	Ser	Arg	Tyr	Tyr	Leu	Ala
1				5					10		

<210> 143

<211> 12

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR1 of MS-Roche#7

<400> 143

Arg	Ala	Ser	Gln	Ser	Val	Ser	Ser	Ser	Tyr	Leu	Ala
1				5					10		

<210> 144

<211> 7

<212> PRT

<213> artificial sequence

50/165

<220>

<223> synthetic construct; LCDR2 of MS-Roche#7

<400> 144

Gly Ala Ser Ser Arg Ala Thr
1 5

<210> 145

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#7

<400> 145

Phe Gln Leu Tyr Ser Asp Pro Phe
1 5

<210> 146

<211> 10

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR1 of MS-Roche#7

<400> 146

Gly Phe Thr Phe Ser Ser Tyr Ala Met Ser
1 5 10

<210> 147

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#7

<400> 147

Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 148

<211> 17

<212> PRT

51/165

<213> artificial sequence

<220>

<223> synthetic construct; HCDR3 of MS-Roche#7

<400> 148

Gly	Lys	Gly	Asn	Thr	His	Lys	Pro	Tyr	Gly	Tyr	Val	Arg	Tyr	Phe	Asp
1				5					10					15	

Val

<210> 149

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#7.1

<400> 149

His	Gln	Leu	Tyr	Ser	Ser	Pro	Tyr
1				5			

<210> 150

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#7.2

<400> 150

Gln	Gln	Ile	Tyr	Ser	Phe	Pro	His
1				5			

<210> 151

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#7.3

<400> 151

His	Gln	Val	Tyr	Ser	His	Pro	Phe
1				5			

<210> 152

<211> 8

52/165

<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#7.4

<400> 152

Gln Gln Ile Tyr Asn Phe Pro His
1 5

<210> 153
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#7.5

<400> 153

His Gln Val Tyr Ser Ser Pro Phe
1 5

<210> 154
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#7.6

<400> 154

His Gln Leu Tyr Ser Pro Pro Tyr
1 5

<210> 155
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#7.7

<400> 155

His Gln Val Tyr Ser Ala Pro Phe
1 5

<210> 156
<211> 8
<212> PRT
<213> artificial sequence

53/165

<220>

<223> synthetic construct; LCDR3 of MS-Roche#7.8

<400> 156

His Gln Val Tyr Ser Phe Pro Ile

1 5

<210> 157

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#7.9

<400> 157

Leu Gln Ile Tyr Asn Met Pro Ile

1 5

<210> 158

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#7.10

<400> 158

Gln Gln Val Tyr Asn Pro Pro His

1 5

<210> 159

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#7.11

<400> 159

Gln Gln Val Tyr Ser Pro Pro His

1 5

<210> 160

<211> 12

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR1 of MS-Roche#7.12

54/165

<400> 160

Arg Ala Ser Gln Tyr Val Ser Ser Pro Tyr Leu Ala
1 5 10

<210> 161

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR2 of MS-Roche#7.12

<400> 161

Gly Ser Ser Asn Arg Ala Thr
1 5

<210> 162

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#7.12

<400> 162

Leu Gln Leu Tyr Asn Ile Pro Asn
1 5

<210> 163

<211> 10

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR1 of MS-Roche#7.12

<400> 163

Gly Phe Thr Phe Ser Ser Tyr Gly Met Ser
1 5 10

<210> 164

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#7.12

<400> 164

Asn Ile Ser Gly Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val Lys

55/165

1 5 10 15

Gly

<210> 165
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR3 of MS-Roche#7.12

<400> 165

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
1 5 10 15

Val

<210> 166
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#7.13

<400> 166

His Gln Val Tyr Ser Pro Pro Phe
1 5

<210> 167
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.2H1

<400> 167

Ala Ile Asn Ala Asn Gly Leu Lys Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 168
<211> 17

56/165

<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.2H2

<400> 168

Ala	Ile	Asn	Gly	Thr	Gly	Met	Lys	Lys	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 169
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.2H3

<400> 169

Ala	Ile	Asn	Ala	Asn	Gly	Tyr	Lys	Thr	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 170
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.2H4

<400> 170

Ala	Ile	Asn	Ser	Lys	Gly	Ser	Arg	Ile	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 171
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.2H5

57/165

<400> 171

Ala Ile Asn Ala Thr Gly Arg Ser Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 172

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#7.2H6

<400> 172

Ala Ile Asn Ala Arg Gly Asn Arg Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 173

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#7.2H7

<400> 173

Ala Ile Asn Ser Arg Gly Ser Asp Thr His Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 174

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#7.2H8

<400> 174

Ala Ile Asn Ala Ser Gly His Lys Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

58/165

Gly

<210> 175
<211> 12
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR1 of MS-Roche#7.2L1

<400> 175

Arg Ala Ser Gln Tyr Val Asp Arg Thr Tyr Leu Ala
1 5 10

<210> 176
<211> 12
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR1 of MS-Roche#7.2L2

<400> 176

Arg Ala Ser Gln Tyr Ile Ser Phe Arg Tyr Leu Ala
1 5 10

<210> 177
<211> 12
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR1 of MS-Roche#7.2L4

<400> 177

Arg Ala Ser Gln Phe Ile Arg Arg Ser Tyr Leu Ala
1 5 10

<210> 178
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#7.3H1

<400> 178

His Gln Val Tyr Ser His Pro Phe

59/165

1 5

<210> 179
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.3H1

<400> 179

Ala Ile Ser Ala Ile Ser Asn Lys Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 180
<211> 12
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR1 of MS-Roche#7.3L1

<400> 180

Arg Ala Ser Gln Tyr Leu His Tyr Gly Tyr Leu Ala
1 5 10

<210> 181
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.4H1

<400> 181

Ala Ile Asn Ala Thr Gly Tyr Arg Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 182
<211> 17
<212> PRT
<213> artificial sequence

<220>

60/165

<223> synthetic construct; HCDR2 of MS-Roche#7.4H2

<400> 182

Ala	Ile	Asn	Tyr	Asn	Gly	Ala	Arg	Ile	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 183

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#7.9H1

<400> 183

Leu	Gln	Ile	Tyr	Asn	Met	Pro	Ile
1				5			

<210> 184

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#7.9H1

<400> 184

Ala	Ile	Asn	Ala	Asn	Gly	Gln	Arg	Lys	Phe	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 185

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#7.9H2

<400> 185

Ala	Ile	Asn	Ala	Asp	Gly	Asn	Arg	Lys	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

61/165

<210> 186
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.9H3

<400> 186

Ala	Ile	Asn	Tyr	Gln	Gly	Asn	Arg	Lys	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5				10						15	

Gly

<210> 187
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.9H4

<400> 187

Ala	Ile	Asn	Ala	Val	Gly	Met	Lys	Lys	Phe	Tyr	Ala	Asp	Ser	Val	Lys
1				5				10						15	

Gly

<210> 188
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.9H5

<400> 188

Ala	Ile	Asn	His	Ala	Gly	Asn	Lys	Lys	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5				10						15	

Gly

<210> 189
<211> 12

62/165

<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR1 of MS-Roche#7.9L1

<400> 189

Arg Ala Ser Gln Arg Leu Ser Pro Arg Tyr Leu Ala
1 5 10

<210> 190
<211> 12
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR1 of MS-Roche#7.9L2

<400> 190

Arg Ala Ser Gln Tyr Leu His Lys Arg Tyr Leu Ala
1 5 10

<210> 191
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.9H6

<400> 191

Ala Ile Asn Ala Ser Gly Arg Leu Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 192
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.9H7

<400> 192

Ala Ile Asn Ala Ser Gly Thr Arg Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

63/165

<210> 193
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.9H8
<400> 193

Ala Ile Asn Ala Ser Gly Ser Lys Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 194
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.9H9
<400> 194

Ala Ile Asn Gly Lys Gly Asn Lys Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 195
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.11H1
<400> 195

Gly Ile Asn Ala Ala Gly Phe Arg Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 196
<211> 17

64/165

<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.11H2

<400> 196

Ala	Ile	Asn	Ala	Asn	Gly	Tyr	Lys	Lys	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 197
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.11H3

<400> 197

Gly	Ile	Asn	Ala	Asn	Gly	Asn	Arg	Thr	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 198
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.11H4

<400> 198

Ala	Ile	Asn	Ala	Asn	Gly	Tyr	Lys	Thr	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 199
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.11H5

65/165

<400> 199

Ala Ile Asn Ala His Gly Gln Arg Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 200

<211> 12

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR1 of MS-Roche#7.11L1

<400> 200

Arg Ala Ser Gln Arg Ile Leu Arg Ile Tyr Leu Ala
1 5 10

<210> 201

<211> 12

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR1 of MS-Roche#7.12H1

<400> 201

Arg Ala Ser Gln Tyr Val Phe Arg Arg Tyr Leu Ala
1 5 10

<210> 202

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#7.12H1

<400> 202

Leu Gln Leu Tyr Asn Ile Pro Asn
1 5

<210> 203

<211> 10

<212> PRT

<213> artificial sequence

<220>

66/165

<223> synthetic construct; HCDR1 of MS-Roche#7.12H1

<400> 203

Gly	Phe	Thr	Phe	Ser	Ser	Tyr	Gly	Met	Ser
1				5				10	

<210> 204

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#7.12H1

<400> 204

Asn	Ile	Asn	Gly	Asn	Gly	Asn	Arg	Lys	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5				10						15	

Gly

<210> 205

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#7.12L1

<400> 205

Asn	Ile	Ser	Gly	Ser	Gly	Ser	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5				10						15	

Gly

<210> 206

<211> 12

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR1 of MS-Roche#7.12L2

<400> 206

Arg	Ala	Ser	Gln	Arg	Phe	Phe	Tyr	Lys	Tyr	Leu	Ala
1				5				10			

<210> 207

67/165

<211> 12
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR1 of MS-Roche#7.12L3

<400> 207

Arg Ala Ser Gln Phe Val Arg Arg Gly Phe Leu Ala
1 5 10

<210> 208
<211> 12
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR1 of MS-Roche#7.12L4

<400> 208

Arg Ala Ser Gln Arg Leu Lys Arg Ser Tyr Leu Ala
1 5 10

<210> 209
<211> 12
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR1 of MS-Roche#7.12L6

<400> 209

Arg Ala Ser Gln Tyr Leu Trp Tyr Arg Tyr Leu Ala
1 5 10

<210> 210
<211> 12
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR1 of MS-Roche#7.12L7

<400> 210

Arg Ala Ser Gln Trp Ile Arg Lys Thr Tyr Leu Ala
1 5 10

<210> 211
<211> 12
<212> PRT
<213> artificial sequence

68/165

<220>

<223> synthetic construct; LCDR1 of MS-Roche#8

<400> 211

Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala
1 5 10

<210> 212

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR2 of MS-Roche#8

<400> 212

Gly Ala Ser Ser Arg Ala Thr
1 5

<210> 213

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#8

<400> 213

Gln Gln Leu Ser Ser Phe Pro Pro
1 5

<210> 214

<211> 10

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR1 of MS-Roche#8

<400> 214

Gly Phe Thr Phe Ser Ser Tyr Ala Met Ser
1 5 10

<210> 215

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#8

69/165

<400> 215

Ala	Ile	Ser	Gly	Ser	Gly	Gly	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 216

<211> 15

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR3 of MS-Roche#8

<400> 216

Leu	Leu	Ser	Arg	Gly	Tyr	Asn	Gly	Tyr	Tyr	His	Lys	Phe	Asp	Val
1				5					10					15

<210> 217

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#8.1

<400> 217

Gln	Gln	Leu	Ser	Asn	Tyr	Pro	Pro
1				5			

<210> 218

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#8.2

<400> 218

Gln	Gln	Leu	Ser	Ser	Tyr	Pro	Pro
1				5			

<210> 219

<211> 17

<212> PRT

<213> artificial sequence

<220>

70/165

<223> synthetic construct; HCDR2 of MS-Roche#8.1H1

<400> 219

Ala	Ile	Ser	Arg	Ser	Gly	Ser	Asn	Ile	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 220

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#8.2H1

<400> 220

Gln	Gln	Leu	Ser	Ser	Tyr	Pro	Pro
1				5			

<210> 221

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#8.2H1

<400> 221

Ala	Ile	Ser	Ile	Thr	Gly	Arg	Arg	Lys	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 222

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#8.2H2

<400> 222

Ala	Ile	Ser	Arg	Thr	Gly	Ser	Lys	Thr	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

71/165

<210> 223
<211> 16
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#8.2H4

<400> 223

Ala Thr Ser Val Lys Gly Lys Thr Tyr Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

<210> 224
<211> 12
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR1 of MS-Roche#8.2L1

<400> 224

Arg Ala Ser Gln Arg Val Ser Gly Arg Tyr Leu Ala
1 5 10

<210> 225
<211> 109
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; VL kappal

<220>
<221> MISC_FEATURE
<222> (96)..(96)
<223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His
, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, or
Tyr

<220>
<221> MISC_FEATURE
<222> (93)..(93)
<223> Xaa = any amino acid of a mixture of Ala, Asp, Gly, His, Leu, Asn
or Ser

<220>
<221> MISC_FEATURE
<222> (92)..(92)
<223> Xaa = any amino acid of a mixture of Asp, Gly, Asn, Ser or Tyr

72/165

<220>
 <221> MISC_FEATURE
 <222> (91)..(91)
 <223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His
 , Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp or Tyr

<220>
 <221> MISC_FEATURE
 <222> (89)..(89)
 <223> Xaa = any amino acid of a mixture of Phe, His, Ile, Leu, Met or G
 ln,

<220>
 <221> MISC_FEATURE
 <222> (85)..(85)
 <223> Xaa = can be Thr or Val

<220>
 <221> MISC_FEATURE
 <222> (94)..(94)
 <223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His
 , Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, or
 Tyr

<220>
 <221> MISC_FEATURE
 <222> (95)..(95)
 <223> Xaa = any amino acid of a mixture of Leu, Pro or Ser

<400> 225

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5					10					15	

Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Gly	Ile	Ser	Ser	Tyr
			20					25					30		

Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
		35					40					45			

Tyr	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55					60				

Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75				80	

Glu	Asp	Phe	Ala	Xaa	Tyr	Tyr	Cys	Xaa	Gln	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
				85					90					95	

73/165

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105

<210> 226
<211> 114
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; VL kappa2

<220>
<221> misc_feature
<222> (101)..(101)
<223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His
, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, or
Tyr

<220>
<221> misc_feature
<222> (94)..(94)
<223> Xaa = any amino acid of a mixture of Phe, His, Ile, Leu, Met or G
ln,

<220>
<221> misc_feature
<222> (96)..(96)
<223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His
, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp or Tyr

<220>
<221> misc_feature
<222> (97)..(97)
<223> Xaa = any amino acid of a mixture of Asp, Gly, Asn, Ser or Tyr

<220>
<221> misc_feature
<222> (98)..(98)
<223> Xaa = any amino acid of a mixture of Ala, Asp, Gly, His, Leu, Asn
or Ser

<220>
<221> misc_feature
<222> (99)..(99)
<223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His
, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, or
Tyr

<220>
<221> misc_feature

74/165

<222> (100)..(100)

<223> Xaa = any amino acid of a mixture of Leu, Pro or Ser

<400> 226

Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Leu	Ser	Leu	Pro	Val	Thr	Pro	Gly
1				5				10				15			

Glu	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Ser	Leu	Leu	His	Ser
			20					25				30			

Asn	Gly	Tyr	Asn	Tyr	Leu	Asp	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser
		35					40					45			

Pro	Gln	Leu	Leu	Ile	Tyr	Leu	Gly	Ser	Asn	Arg	Ala	Ser	Gly	Val	Pro
	50					55					60				

Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile
65					70					75					80

Ser	Arg	Val	Glu	Ala	Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Xaa	Gln	Xaa
			85					90						95	

Xaa	Xaa	Xaa	Xaa	Xaa	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys
			100					105					110		

Arg Thr

<210> 227

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL kappa3

<220>

<221> misc_feature

<222> (97)..(97)

<223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, or Tyr

<220>

<221> misc_feature

<222> (90)..(90)

<223> Xaa = any amino acid of a mixture of Phe, His, Ile, Leu, Met or Gln,

75/165

<220>
 <221> misc_feature
 <222> (86)..(86)
 <223> Xaa = Thr or Val

<220>
 <221> misc_feature
 <222> (92)..(92)
 <223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His
 , Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp or Tyr

<220>
 <221> misc_feature
 <222> (93)..(93)
 <223> Xaa = any amino acid of a mixture of Asp, Gly, Asn, Ser or Tyr

<220>
 <221> misc_feature
 <222> (94)..(94)
 <223> Xaa = any amino acid of a mixture of Ala, Asp, Gly, His, Leu, Asn
 or Ser

<220>
 <221> misc_feature
 <222> (95)..(95)
 <223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His
 , Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, or
 Tyr

<220>
 <221> misc_feature
 <222> (96)..(96)
 <223> Xaa = any amino acid of a mixture of Leu, Pro or Ser

<400> 227

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
 50 55 60

76/165

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
 65 70 75 80

Pro Glu Asp Phe Ala Xaa Tyr Tyr Cys Xaa Gln Xaa Xaa Xaa Xaa Xaa
 85 90 95

Xaa Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
 100 105 110

<210> 228
 <211> 115
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; VL kappa4

<220>
 <221> MISC_FEATURE
 <222> (102)..(102)
 <223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, or Tyr

<220>
 <221> MISC_FEATURE
 <222> (95)..(95)
 <223> Xaa = any amino acid of a mixture of Phe, His, Ile, Leu, Met or Gln,

<220>
 <221> MISC_FEATURE
 <222> (97)..(97)
 <223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp or Tyr

<220>
 <221> MISC_FEATURE
 <222> (98)..(98)
 <223> Xaa = any amino acid of a mixture of Asp, Gly, Asn, Ser or Tyr

<220>
 <221> MISC_FEATURE
 <222> (99)..(99)
 <223> Xaa = any amino acid of a mixture of Ala, Asp, Gly, His, Leu, Asn or Ser

<220>
 <221> MISC_FEATURE
 <222> (100)..(100)

77/165

<223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, or Tyr

<220>

<221> MISC_FEATURE

<222> (101)..(101)

<223> Xaa = any amino acid of a mixture of Leu, Pro or Ser

<400> 228

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Arg Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Xaa Gln
85 90 95

Xaa Xaa Xaa Xaa Xaa Xaa Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys Arg Thr
115

<210> 229

<211> 111

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL lambda1

<220>

<221> MISC_FEATURE

<222> (99)..(99)

<223> Xaa = any amino acid

78/165

<220>
 <221> MISC_FEATURE
 <222> (97)..(98)
 <223> Xaa = any amino acid except a Cys or a deletion

<220>
 <221> MISC_FEATURE
 <222> (94)..(96)
 <223> Xaa = any amino acid except a Cys

<220>
 <221> MISC_FEATURE
 <222> (92)..(92)
 <223> Xaa = any amino acid of Cys, Phe, His, Arg, Trp or Tyr

<400> 229

Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
 1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
 20 25 30

Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
 35 40 45

Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
 50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
 65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Xaa Asp Xaa Xaa Xaa
 85 90 95

Xaa Xaa Xaa Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
 100 105 110

<210> 230
 <211> 112
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; VL lambda2

<220>
 <221> MISC_FEATURE
 <222> (100)..(100)

79/165

<223> Xaa = any amino acid

<220>

<221> MISC_FEATURE

<222> (93)..(93)

<223> Xaa = any amino acid of Cys, Phe, His, Arg, Trp or Tyr

<220>

<221> MISC_FEATURE

<222> (95)..(97)

<223> Xaa = any amino acid except a Cys

<220>

<221> MISC_FEATURE

<222> (98)..(99)

<223> Xaa = any amino acid except a Cys or a deletion

<400> 230

Asp	Ile	Ala	Leu	Thr	Gln	Pro	Ala	Ser	Val	Ser	Gly	Ser	Pro	Gly	Gln
1				5				10						15	

Ser	Ile	Thr	Ile	Ser	Cys	Thr	Gly	Thr	Ser	Ser	Asp	Val	Gly	Gly	Tyr
		20					25						30		

Asn	Tyr	Val	Ser	Trp	Tyr	Gln	Gln	His	Pro	Gly	Lys	Ala	Pro	Lys	Leu
		35				40						45			

Met	Ile	Tyr	Asp	Val	Ser	Asn	Arg	Pro	Ser	Gly	Val	Ser	Asn	Arg	Phe
	50					55					60				

Ser	Gly	Ser	Lys	Ser	Gly	Asn	Thr	Ala	Ser	Leu	Thr	Ile	Ser	Gly	Leu
65					70					75					80

Gln	Ala	Glu	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Ser	Xaa	Asp	Xaa	Xaa
				85					90					95	

Xaa	Xaa	Xaa	Xaa	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu	Gly
				100				105					110		

<210> 231

<211> 109

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL lambda3

80/165

<220>
<221> MISC_FEATURE
<222> (97)..(97)
<223> Xaa = any amino acid

<220>
<221> MISC_FEATURE
<222> (90)..(90)
<223> Xaa = any amino acid of Cys, Phe, His, Arg, Trp or Tyr

<220>
<221> MISC_FEATURE
<222> (92)..(94)
<223> Xaa = any amino acid except a Cys

<220>
<221> MISC_FEATURE
<222> (95)..(96)
<223> Xaa = any amino acid except a Cys or a deletion

<400> 231

Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Xaa Asp Xaa Xaa Xaa Xaa Xaa
85 90 95

Xaa Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105

<210> 232
<211> 127
<212> PRT
<213> artificial sequence

82/165

Xaa Xaa Asp Xaa Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 233
 <211> 127
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; VH1B

<220>
 <221> MISC_FEATURE
 <222> (99)..(112)
 <223> Xaa = any amino acid or a deletion

<220>
 <221> MISC_FEATURE
 <222> (113)..(113)
 <223> Xaa = any amino acid

<220>
 <221> MISC_FEATURE
 <222> (114)..(114)
 <223> Xaa = any amino acid out of a mixture of Ala, Asp, Glu, Phe, Gly, Ile, Leu, Met, Pro, Gln, Ser, Thr, Val or Tyr

<220>
 <221> MISC_FEATURE
 <222> (116)..(116)
 <223> Xaa = any amino acid out of a mixture of Phe, His, Ile, Leu, Asn, Pro, Ser, Val, Trp or Tyr

<400> 233

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
 65 70 75 80

83/165

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 100 105 110

Xaa Xaa Asp Xaa Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 234
 <211> 128
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; VH2

<220>
 <221> MISC_FEATURE
 <222> (100)..(113)
 <223> Xaa = any amino acid or a deletion

<220>
 <221> MISC_FEATURE
 <222> (114)..(114)
 <223> Xaa = any amino acid

<220>
 <221> MISC_FEATURE
 <222> (117)..(117)
 <223> Xaa = any amino acid out of a mixture of Phe, His, Ile, Leu, Asn,
 Pro, Ser, Val, Trp or Tyr

<220>
 <221> MISC_FEATURE
 <222> (115)..(115)
 <223> Xaa = any amino acid out of a mixture of Ala, Asp, Glu, Phe, Gly,
 Ile, Leu, Met, Pro, Gln, Ser, Thr, Val or Tyr

<400> 234

Gln Val Gln Leu Lys Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
 1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
 20 25 30

Gly Val Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
 35 40 45

84/165

Trp Leu Ala Leu Ile Asp Trp Asp Asp Asp Lys Tyr Tyr Ser Thr Ser
 50 55 60

Leu Lys Thr Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
 65 70 75 80

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
 85 90 95

Cys Ala Arg Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 100 105 110

Xaa Xaa Xaa Asp Xaa Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 235
 <211> 127
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; VH3

<220>
 <221> MISC_FEATURE
 <222> (99)..(112)
 <223> Xaa = any amino acid or a deletion

<220>
 <221> MISC_FEATURE
 <222> (113)..(113)
 <223> Xaa = any amino acid

<220>
 <221> MISC_FEATURE
 <222> (116)..(116)
 <223> Xaa = any amino acid out of a mixture of Phe, His, Ile, Leu, Asn,
 Pro, Ser, Val, Trp or Tyr

<220>
 <221> MISC_FEATURE
 <222> (114)..(114)
 <223> Xaa = any amino acid out of a mixture of Ala, Asp, Glu, Phe, Gly,
 Ile, Leu, Met, Pro, Gln, Ser, Thr, Val or Tyr

<400> 235

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1					5					10					15				
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr				
			20				25						30						
Ala	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val				
			35				40						45						
Ser	Ala	Ile	Ser	Gly	Ser	Gly	Gly	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val				
			50				55						60						
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr				
65				70						75						80			
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys				
			85						90						95				
Ala	Arg	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa				
			100						105						110				
Xaa	Xaa	Asp	Xaa	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser					
			115			120						125							

<210>	236
<211>	126
<212>	PRT
<213>	artificial sequence

```
<220>
<223> synthetic construct; VH4
```

```

<220>
<221> MISC_FEATURE
<222> (98)..(111)
<223> Xaa = any amino acid or a deletion

```

```
<220>
<221> MISC_FEATURE
<222> (112)..(112)
<223> Xaa = any amino acid
```

```

<220>
<221> MISC_FEATURE
<222> (113)..(113)
<223> Xaa = any amino acid out of a mixture of Ala, Asp, Glu, Phe, Gly,
      Ile, Leu, Met, Pro, Gln, Ser, Thr, Val or Tyr

```

 $\langle 220 \rangle$

86/165

<221> MISC_FEATURE
 <222> (115)..(115)
 <223> Xaa = any amino acid out of a mixture of Phe, His, Ile, Leu, Asn,
 Pro, Ser, Val, Trp or Tyr

<400> 236

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
 1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
 20 25 30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45

Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
 50 55 60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
 65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
 85 90 95

Arg Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 100 105 110

Xaa Asp Xaa Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 237
 <211> 127
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; VH5

<220>
 <221> MISC_FEATURE
 <222> (99)..(112)
 <223> Xaa = any amino acid or a deletion

<220>
 <221> MISC_FEATURE
 <222> (113)..(113)
 <223> Xaa = any amino acid

87/165

<220>
<221> MISC_FEATURE
<222> (116)..(116)
<223> Xaa = any amino acid out of a mixture of Phe, His, Ile, Leu, Asn,
Pro, Ser, Val, Trp or Tyr

<220>
<221> MISC_FEATURE
<222> (114)..(114)
<223> Xaa = any amino acid out of a mixture of Ala, Asp, Glu, Phe, Gly,
Ile, Leu, Met, Pro, Gln, Ser, Thr, Val or Tyr

<400> 237

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Asp Xaa Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 238
<211> 130
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; VH6

<220>
<221> MISC_FEATURE

88/165

<222> (102)..(115)

<223> Xaa = any amino acid or a deletion

<220>

<221> MISC_FEATURE

<222> (116)..(116)

<223> Xaa = any amino acid

<220>

<221> MISC_FEATURE

<222> (119)..(119)

<223> Xaa = any amino acid out of a mixture of Phe, His, Ile, Leu, Asn, Pro, Ser, Val, Trp or Tyr

<220>

<221> MISC_FEATURE

<222> (117)..(117)

<223> Xaa = any amino acid out of a mixture of Ala, Asp, Glu, Phe, Gly, Ile, Leu, Met, Pro, Gln, Ser, Thr, Val or Tyr

<400> 238

Gln	Val	Gln	Leu	Gln	Gln	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln
1			5						10					15	

Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Ser	Asn
			20					25					30		

Ser	Ala	Ala	Trp	Asn	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
		35					40					45			

Trp	Leu	Gly	Arg	Thr	Tyr	Tyr	Arg	Ser	Lys	Trp	Tyr	Asn	Asp	Tyr	Ala
	50					55					60				

Val	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
65					70					75					80

Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
			85						90					95	

Tyr	Tyr	Cys	Ala	Arg	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
			100				105						110		

Xaa	Xaa	Xaa	Xaa	Xaa	Asp	Xaa	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val
		115					120					125			

Ser Ser

130

<210> 239
<211> 327
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct; VL kappa1

<220>
<221> misc_feature
<222> (286)..(288)
<223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT,
CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
<221> misc_feature
<222> (271)..(273)
<223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CAG,
CGT, TCT, ACT, GTT, TGG or TAT

<220>
<221> misc_feature
<222> (265)..(267)
<223> nnn = TTT, CAT, CTT, ATG or CAG

<220>
<221> misc_feature
<222> (253)..(256)
<223> nnn = can be ACT or GTT

<220>
<221> misc_feature
<222> (283)..(285)
<223> nnn = CTT, CCT or TCT

<220>
<221> misc_feature
<222> (280)..(282)
<223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT,
CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
<221> misc_feature
<222> (277)..(279)
<223> nnn = GCT, GAT, GGT, CAT, CTT, AAT or TCT

<220>
<221> misc_feature
<222> (274)..(276)

90/165

<223> nnn = GAT, GGT, AAT, TCT or TAT

<400> 239
gatatccaga tgaccagag cccgtctagc ctgagcgoga gcgtgggtga tcgtgtgacc 60
attacctgca gagcgagcca gggcattagc agctatctgg cgtggtacca gcagaaacca 120
ggtaaagcac cgaaactatt aatttatgca gccagcagct tgcaaagcgg ggtcccgtcc 180
cgttttagcg gctctggatc cggcactgat tttaacctga ccattagcag cctgcaacct 240
gaagactttg cgnnntatta ttgcnnncag nnnnnnnnnn nnnnnnnnac ctttgccag 300
ggtacgaaag ttgaaattaa acgtacg 327

<210> 240

<211> 328

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VL kappa2

<220>

<221> misc_feature

<222> (289)..(289)

<223> n = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, C
AG, CGT, TCT, ACT, GTT, TGG or TAT

<220>

<221> misc_feature

<222> (280)..(280)

<223> n = TTT, CAT, CTT, ATG or CAG

<220>

<221> misc_feature

<222> (284)..(284)

<223> n = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CAG, C
GT, TCT, ACT, GTT, TGG or TAT

<220>

<221> misc_feature

<222> (285)..(285)

<223> n = GAT, GGT, AAT, TCT or TAT

<220>

<221> misc_feature

<222> (286)..(289)

<223> n = GCT, GAT, GGT, CAT, CTT, AAT or TCT

<220>

<221> misc_feature

91/165

<222> (287)..(287)
 <223> n = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (288)..(288)
 <223> n = CTT, CCT or TCT

<400> 240
 gatatcgtga tgacccagag ccactgagc ctgccagtga ctccgggcga gcctgcgagc 60
 attagctgca gaagcagcca aagcctgctg catagcaacg gctataacta tctggattgg 120
 taccttcaaa aaccaggtca aagcccgag ctattaattt atctgggcag caaccgtgcc 180
 agtgggggtcc cggatcgttt tagcggctct ggatccggca ccgattttac cctgaaaatt 240
 agccgtgtgg aagctgaaga cgtgggcgtg tattattgcn cagnnnnnna cctttggcca 300
 gggtacgaaa gttgaaatta aacgtacg 328

<210> 241
 <211> 330
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VL kappa3

<220>
 <221> misc_feature
 <222> (289)..(291)
 <223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (256)..(258)
 <223> nnn = can be ACT or GTT

<220>
 <221> misc_feature
 <222> (265)..(276)
 <223> nnn = TTT, CAT, CTT, ATG or CAG

<220>
 <221> misc_feature
 <222> (274)..(276)
 <223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

92/165

<220>
<221> misc_feature
<222> (277)..(279)
<223> nnn = GAT, GGT, AAT, TCT or TAT

<220>
<221> misc_feature
<222> (280)..(282)
<223> nnn = GCT, GAT, GGT, CAT, CTT, AAT or TCT

<220>
<221> misc_feature
<222> (283)..(285)
<223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT,
CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
<221> misc_feature
<222> (286)..(288)
<223> nnn = CTT, CCT or TCT

<400> 241
gatatcgtgc tgacccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc 60
ctgagctgca gagcgagcca gagcgtgagc agcagctatc tggcgtggta ccagcagaaa 120
ccaggtcaag caccgcgtct attaatttat ggcgcgagca gccgtgcaac tgggggtcccg 180
gcgcgtttta gcggctcttg atccggcacg gattttaccc tgaccattag cagcctggaa 240
cctgaagact ttgcgnnnta ttattgcnnn cagnnnnnnn nnnnnnnnnn nacctttggc 300
cagggtacga aagttgaaat taaacgtacg 330

<210> 242
<211> 345
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct; VL kappa4

<220>
<221> misc_feature
<222> (304)..(306)
<223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT,
CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
<221> misc_feature
<222> (283)..(285)
<223> nnn = TTT, CAT, CTT, ATG or CAG

93/165

<220>
<221> misc_feature
<222> (289)..(291)
<223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CAG,
CGT, TCT, ACT, GTT, TGG or TAT

<220>
<221> misc_feature
<222> (292)..(294)
<223> nnn = GAT, GGT, AAT, TCT or TAT

<220>
<221> misc_feature
<222> (295)..(297)
<223> nnn = GCT, GAT, GGT, CAT, CTT, AAT or TCT

<220>
<221> misc_feature
<222> (298)..(300)
<223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT,
CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
<221> misc_feature
<222> (301)..(303)
<223> nnn = CTT, CCT or TCT

<400> 242
gatatcgtga tgacccagag cccggatagc ctggcgggtga gcctggggcga acgtgcgacc 60
attaactgca gaagcagcca gagcgtgctg tatagcagca acaacaaaaa ctatctggcg 120
tggtaccagc agaaaccagg tcagccgccg aaactattaa tttattgggc atccaccgct 180
gaaagcgggg tcccggatcg ttttagcggc tctggatccg gcaactgattt taccctgacc 240
atttcgtccc tgcaagctga agacgtggcg gtgtattatt gcnnncagnn nnnnnnnnnn 300
nnnnnnacct ttggccaggg tacgaaagtt gaaattaaac gtacg 345

<210> 243
<211> 322
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct; VL lambda1

<220>
<221> misc_feature
<222> (274)..(274)
<223> n = TGT, TTT, CAT, CGT, TGG or TAT

94/165

<220>
<221> misc_feature
<222> (278)..(280)
<223> n = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, C
AG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
<221> misc_feature
<222> (281)..(282)
<223> n = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, C
AG, CGT, TCT, ACT, GTT, TGG or TAT or a deletion

<220>
<221> misc_feature
<222> (283)..(283)
<223> n = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, C
CT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<400> 243
gatatcgtgc tgaccagacc gccttcagtg agtggcgcac caggtcagcg tgtgaccatc 60
tcgtgtagcg gcagcagcag caacattggc agcaactatg tgagctggta ccagcagttg 120
cccgggacgg cgccgaaact gctgatttat gataacaacc agcgtccctc aggcgtgccg 180
gatcgtttta gcggatccaa aagcggcacc agcgcgagcc ttgcgattac gggcctgcaa 240
agcgaagacg aagcggatta ttattgccag tctngatnnn nnngtgtttg gcggcggcac 300
gaagttaacc gttcttggcc ag 322

<210> 244
<211> 336
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct; VL lambda2

<220>
<221> misc_feature
<222> (274)..(276)
<223> nnn = TGT, TTT, CAT, CGT, TGG or TAT

<220>
<221> misc_feature
<222> (290)..(295)
<223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT,
CAG, CGT, TCT, ACT, GTT, TGG or TAT or a deletion

<220>

95/165

<221> misc_feature
 <222> (296)..(298)
 <223> nnn = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT,
 CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (280)..(289)
 <223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT,
 CAG, CGT, TCT, ACT, GTT, TGG or TAT

<400> 244
 gatatcgcac tgaccagccc agcttcagtg agcggctcac caggtcagag cattaccatc 60
 tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag 120
 catcccggga aggcgcgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg 180
 agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240
 caagcggaag acgaagcgga ttattattgc cagnnngatn nnnnnnnnnn nnnnnnngtg 300
 tttggcggcg gcacgaagtt aaccgttcct ggccag 336

<210> 245
 <211> 327
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VL lambda3

<220>
 <221> misc_feature
 <222> (265)..(267)
 <223> nnn = TGT, TTT, CAT, CGT, TGG or TAT

<220>
 <221> misc_feature
 <222> (286)..(288)
 <223> nnn = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT,
 CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (280)..(285)
 <223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT,
 CAG, CGT, TCT, ACT, GTT, TGG or TAT or a deletion

<220>
 <221> misc_feature
 <222> (271)..(279)
 <223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT,

96/165

CAG, CGT, TCT, ACT, GTT, TGG or TAT

```

<400> 245
gatatcgaac tgaccagcc gccttcagtg agcgttgac caggtcagac cgcgcgtatc      60
tcgtgtagcg gcgatgcgct gggcgataaa tacgcgagct ggtaccagca gaaaccggg      120
caggcgccag ttctggtgat ttatgatgat tctgaccgtc cctcaggcat cccggaacgc      180
tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa      240
gacgaagcgg attattattg ccagnnngat nnnnnnnnnn nnnnnnnngt gtttggcggc      300
ggcacgaagt taaccgttct tggccag                                           327

```

```

<210> 246
<211> 382
<212> DNA
<213> artificial sequence

```

```

<220>
<223> synthetic construct; VH1A

```

```

<220>
<221> misc_feature
<222> (345)..(347)
<223> nnn = TTT, CAT, ATT, CTT, AAT, CCT, TCT, GTT, TGG or TAT

```

```

<220>
<221> misc_feature
<222> (339)..(341)
<223> nnn = GCT, GAT, GAG, TTT, GGT, ATT, CTT, ATG, CCT, CAG, TCT, ACT,
      GTT or TAT

```

```

<220>
<221> misc_feature
<222> (336)..(338)
<223> nnn = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT,
      CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

```

```

<220>
<221> misc_feature
<222> (295)..(335)
<223> nnn = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT,
      CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT or a deletion

```

```

<400> 246
caggtgcaat tggttcagtc tggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagt      60
agctgcaaag cctccggagg cacttttagc agctatgcga ttagctgggt gcgccaagcc      120
cctgggcagg gtctcgagtg gatgggcggc attattccga tttttggcac ggcgaactac      180

```

97/165

```

gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat      240
atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtnnnnnn      300
nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn ngatnnntgg ggccaaggca      360
ccctgggtgac ggtagctca gc                                              382

```

```

<210> 247
<211> 383
<212> DNA
<213> artificial sequence

```

```

<220>
<223> synthetic construct; VH1B

```

```

<220>
<221> misc_feature
<222> (346)..(348)
<223> nnn = TTT, CAT, ATT, CTT, AAT, CCT, TCT, GTT, TGG or TAT

```

```

<220>
<221> misc_feature
<222> (295)..(336)
<223> nnn = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT,
      CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT or a deletion

```

```

<220>
<221> misc_feature
<222> (337)..(339)
<223> nnn = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT,
      CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

```

```

<220>
<221> misc_feature
<222> (340)..(342)
<223> nnn = GCT, GAT, GAG, TTT, GGT, ATT, CTT, ATG, CCT, CAG, TCT, ACT,
      GTT or TAT

```

```

<400> 247
caggtgcaat tggttcagag cggcgcgga gtgaaaaaac cgggcgcgag cgtgaaagt      60
agctgcaaag cctccggata tacctttacc agctattata tgcactgggt ccgccaagcc      120
cctgggcagg gtctcgagt gatgggctgg attaaccoga atagcggcgg cacgaactac      180
gcgcagaagt ttcagggccg ggtgaccatg acccgtgata ccagcattag caccgcgtat      240
atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtnnnnnn      300
nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nngatnnntg gggccaaggc      360
accctgggtga cggtagctc agc                                              383

```


98/165

<210> 248
 <211> 386
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VH2

<220>
 <221> misc_feature
 <222> (349)..(351)
 <223> nnn = TTT, CAT, ATT, CTT, AAT, CCT, TCT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (298)..(339)
 <223> nnn = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT,
 CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT or a deletion

<220>
 <221> misc_feature
 <222> (340)..(342)
 <223> nnn = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT,
 CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (343)..(345)
 <223> nnn = GCT, GAT, GAG, TTT, GGT, ATT, CTT, ATG, CCT, CAG, TCT, ACT,
 GTT or TAT

<400> 248
 caggtgcaat tgaaagaaag cggcccggcc ctggtgaaac cgacccaaac cctgaccctg 60
 acctgtacct ttccggatt tagcctgtcc acgtctggcg ttggcgtggg ctggattcgc 120
 cagccgcctg ggaaagccct cgagtggctg gctctgattg attgggatga tgataagtat 180
 tatagcacca gcctgaaaac gcgtctgacc attagcaaag atacttcgaa aaatcaggtg 240
 gtgctgacta tgaccaacat ggacccggtg gatacggcca cctattattg cgcgcgtnnn 300
 nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnngatnn ntggggccaa 360
 ggcaccctgg tgacggttag ctcage 386

<210> 249
 <211> 349
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VH3

99/165

<220>
<221> misc_feature
<222> (314)..(314)
<223> n = TTT, CAT, ATT, CTT, AAT, CCT, TCT, GTT, TGG or TAT

<220>
<221> misc_feature
<222> (295)..(308)
<223> n = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, C
CT, CAG, CGT, TCT, ACT, GTT, TGG or TAT or a deletion

<220>
<221> misc_feature
<222> (309)..(309)
<223> n = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, C
CT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
<221> misc_feature
<222> (310)..(310)
<223> n = GCT, GAT, GAG, TTT, GGT, ATT, CTT, ATG, CCT, CAG, TCT, ACT, G
TT or TAT

<400> 249
caggtgcaat tgggtggaaag cggcgggcggc ctggtgcaac cgggcggcag cctgcgtctg 60
agctgcgcgg cctccggatt taccttttagc agctatgcga tgagctgggt gcgccaagcc 120
cctgggaagg gtctcgagtg ggtgagcgcg attagcggta gcggcggcag cacctattat 180
gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240
ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtnnnnnn 300
nnnnnnnnnn gatntggggc caaggcaccc tggtgacggt tagctcagc 349

<210> 250
<211> 346
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct; VH4

<220>
<221> misc_feature
<222> (311)..(311)
<223> n = TTT, CAT, ATT, CTT, AAT, CCT, TCT, GTT, TGG or TAT

<220>
<221> misc_feature
<222> (292)..(305)

100/165

<223> n = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, C
CT, CAG, CGT, TCT, ACT, GTT, TGG or TAT or a deletion

<220>

<221> misc_feature

<222> (306)..(306)

<223> n = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, C
CT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>

<221> misc_feature

<222> (307)..(307)

<223> n = GCT, GAT, GAG, TTT, GGT, ATT, CTT, ATG, CCT, CAG, TCT, ACT, G
TT or TAT

<400> 250

caggtgcaat tgcaagaaag tgggtccgggc ctggtgaaac cgagcgaaac cctgagcctg	60
acctgcaccg tttccggagg cagcattagc agctattatt ggagctggat tcgccagccg	120
cctgggaagg gtctcgagtg gattggctat atttattata gcggcagcac caactataat	180
ccgagcctga aaagccgggt gaccattagc gttgatactt cgaaaaacca gtttagcctg	240
aaactgagca gcgtgacggc ggcggatacg gccgtgtatt attgcgcgcg tnnnnnnnnn	300
nnnnnnngat ntggggccaa ggcaccctgg tgacgggttag ctgagc	346

<210> 251

<211> 349

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VH5

<220>

<221> misc_feature

<222> (314)..(314)

<223> n = TTT, CAT, ATT, CTT, AAT, CCT, TCT, GTT, TGG or TAT

<220>

<221> misc_feature

<222> (295)..(304)

<223> n = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, C
CT, CAG, CGT, TCT, ACT, GTT, TGG or TAT or a deletion

<220>

<221> misc_feature

<222> (305)..(307)

<223> n = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, C
CT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

101/165

<220>
 <221> misc_feature
 <222> (308)..(310)
 <223> n = GCT, GAT, GAG, TTT, GGT, ATT, CTT, ATG, CCT, CAG, TCT, ACT, G
 TT or TAT

<400> 251
 caggtgcaat tggttcagag cggcgcgga gtgaaaaaac cgggcgaaag cctgaaaatt 60
 agctgcaaag gttccggata ttcctttacg agctattgga ttggctgggt gcgccagatg 120
 cctgggaagg gtctcgagtg gatgggcatt atttatccgg gcgatagcga taccggttat 180
 tctccgagct ttcagggcca ggtgaccatt agcgcgga aaagcattag caccgcgtat 240
 cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgtnnnnnn 300
 nnnnnnnnnn gatntggggc caaggcaccc tggtgacggt tagctcagc 349

<210> 252
 <211> 392
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VH6

<220>
 <221> misc_feature
 <222> (355)..(357)
 <223> nnn = TTT, CAT, ATT, CTT, AAT, CCT, TCT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (304)..(345)
 <223> nnn = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT,
 CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT or a deletion

<220>
 <221> misc_feature
 <222> (346)..(348)
 <223> nnn = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT,
 CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (349)..(351)
 <223> nnn = GCT, GAT, GAG, TTT, GGT, ATT, CTT, ATG, CCT, CAG, TCT, ACT,
 GTT or TAT

<400> 252
 caggtgcaat tgcaacagtc tgggtccggc ctggtgaaac cgagccaaac cctgagcctg 60

102/165

```

acctgtgcga tttccggaga tagcgtgagc agcaacagcg cggcgtggaa ctggattcgc 120
cagtctcctg ggcgtaggct cgagtggtcg ggccgtacct attatcgtag caaatggtat 180
aacgattatg cggtagagcg gaaaagccgg attaccatca acccgatac ttcgaaaaac 240
cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300
cgtnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn ngatnnntgg 360
ggccaaggca ccctggtgac ggtagctca gc 392

```

<210> 253

<211> 4151

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; pMORPH 18 Fab_5'

<400> 253

```

tctagataac gagggcaaaa aatgaaaaag acagctatcg cgattgcagt ggcactggct 60
ggtttcgcta ccgtagcgca ggccgatatc gtgctgacct agagcccggc gaccctgagc 120
ctgtctccgg gcgaacgtgc gaccctgagc tgcagagcga gccagagcgt gagcagcagc 180
tatctggcgt ggtaccagca gaaaccaggt caagcaccgc gtctattaat ttatggcgcg 240
agcagccgtg caactggggg cccggcgcgt ttagcggct ctggatccgg cacggatttt 300
accctgacca ttagcagcct ggaacctgaa gactttgcgg tgtattattg ccagcagcat 360
tataccaccc cgccgacctt tggccagggt acgaaagttg aaattaaacg tacggtggct 420
gctccgagcg tgtttatttt tccgccgagc gatgaacaac tgaaaagcgg cacggcgagc 480
gtggtgtgcc tgctgaacaa cttttatccg cgtgaagcga aagttcagtg gaaagtagac 540
aacgcgtgc aaagcggcaa cagccaggaa agcgtgaccg aacaggatag caaagatagc 600
acctattctc tgagcagcac cctgaccctg agcaaagcgg attatgaaaa acataaagtg 660
tatgcgtgcg aagtgacctc tcaaggctcg agcagccgg tgactaaatc ttttaatcgt 720
ggcgaggcct gataagcatg cgtaggagaa aataaaatga aacaaagcac tattgcaactg 780
gcactcttac cgttgctctt caccctgtt accaaagccg aagtgcatt ggtggaaagc 840
ggcggcggcc tgggtgaacc gggcggcagc ctgcgtctga gctgcgcggc ctccgattt 900
accttttagca gctatgcgat gagctgggtg cgccaagccc ctgggaaggg tctcgagtgg 960
gtgagcgcgga ttagcggtag cggcggcagc acctattatg cggatagcgt gaaaggccgt 1020
tttaccatth cacgtgataa ttcgaaaaac acctgtatc tgcaaatgaa cagcctgcgt 1080

```

103/165

gcggaagata	cggccgtgta	ttattgcgcg	cgttggggcg	gcgatggctt	ttatgcgatg	1140
gattattggg	gccaaggcac	cctggtgacg	gttagctcag	cgtcgaccaa	aggtccaagc	1200
gtgtttccgc	tggtctccgag	cagcaaaagc	accagcggcg	gcacggctgc	cctgggctgc	1260
ctggttaaag	attatttccc	ggaaccagtc	accgtgagct	ggaacagcgg	ggcgtgacc	1320
agcggcgtgc	atacctttcc	ggcggtgctg	caaagcagcg	gcctgtatag	cctgagcagc	1380
gttgtgaccg	tgccgagcag	cagcttaggc	actcagacct	atatttgcaa	cgtgaaccat	1440
aaaccgagca	acaccaaagt	ggataaaaaa	gtggaaccga	aaagcgaatt	cgggggaggg	1500
agcgggagcg	gtgattttga	ttatgaaaag	atggcaaacg	ctaataaggg	ggctatgacc	1560
gaaaatgccg	atgaaaacgc	gctacagtct	gacgctaaag	gcaaacttga	ttctgtcgct	1620
actgattacg	gtgctgctat	cgatggtttc	attggtgacg	tttccggcct	tgctaattgg	1680
aatggtgcta	ctggtgattt	tgtcggctct	aattcccaaa	tggtcgaagt	cggtgacggg	1740
gataattcac	ctttaatgaa	taatttccgt	caatatttac	cttccctccc	tcaatcggtt	1800
gaatgtcgcc	cttttgtctt	tggcgtgggt	aaaccatatg	aattttctat	tgattgtgac	1860
aaaataaact	tattccgtgg	tgtctttgcg	tttcttttat	atgttgccac	ctttatgtat	1920
gtattttcta	cgtttgctaa	catactgcgt	aataaggagt	cttgataagc	ttgacctgtg	1980
aagtgaaaaa	tggcgcagat	tgtgcgacat	tttttttgtc	tgccgtttta	tgaaattgta	2040
aacgttaata	ttttgttaaa	attcgcgtta	aatttttgtt	aaatcagctc	attttttaac	2100
caataggccg	aaatcggcaa	aatcccttat	aatcaaaaag	aatagaccga	gatagggttg	2160
agtgttgttc	cagtttgga	caagagtcca	ctattaaaga	acgtggactc	caacgtcaaa	2220
gggcgaaaaa	cgtctatca	ggcgcgtg	ccactacgag	aaccatcacc	ctaatcaagt	2280
tttttggggg	cgaggtgccg	taaagcacta	aatcggaacc	ctaaaggag	ccccgattt	2340
agagcttgac	ggggaaagcc	ggcgaacgtg	gcgagaaagg	aagggaagaa	agcgaaagga	2400
gcgggcgcta	gggcgtggc	aagtgtagcg	gtcacgctgc	gcgtaaccac	cacaccgcc	2460
gcgcttaatg	cgccgtaca	gggcgcgtgc	tagccatgtg	agcaaaaggc	cagcaaaagg	2520
ccaggaaccg	taaaaaggcc	gcgttgctgg	cgtttttcca	taggctccgc	ccccctgacg	2580
agcatcacia	aaatcgacgc	tcaagtcaga	ggtggcgaaa	cccgcagga	ctataaagat	2640
accaggcggt	tccccctgga	agctccctcg	tgcgtctctc	tgttccgacc	ctgccgctta	2700
ccggatacct	gtccgccttt	ctcccttcgg	gaagcgtggc	gctttctcat	agctcacgct	2760
gtaggtatct	cagttcgggtg	taggtcgttc	gctccaagct	gggctgtgtg	cacgaacccc	2820
ccgttcagtc	cgaccgctgc	gccttatccg	gtaactatcg	tcttgagtcc	aaccgggtaa	2880

104/165

```

gacacgactt atcgccactg gcagcagcca ctggtaacag gattagcaga gcgaggatatg 2940
taggcggtgc tacagagttc ttgaagtggg gccctaacta cggctacact agaagaacag 3000
tatttggtat ctgcgctctg ctgtagccag ttaccttcgg aaaaagagtt ggtagctctt 3060
gatccggcaa acaaaccacc gctggtagcg gtggtttttt tgtttgcaag cagcagatta 3120
cgcgcagaaa aaaaggatct caagaagatc ctttgatctt ttctacgggg tctgacgctc 3180
agtggaacga aaactcacgt taagggaattt tggtcagatc tagcaccagg cgtttaaggg 3240
caccaataac tgccttaaaa aaattacgcc ccgccctgcc actcatcgca gtactgttgt 3300
aattcattaa gcattctgcc gacatggaag ccatcacaaa cggcatgatg aacctgaatc 3360
gccagcggca tcagcacctt gtcgccttgc gtataatatt tgcccatagt gaaaacgggg 3420
gcgaagaagt tgtccatatt ggctacgttt aaatcaaaac tggtgaaact caccagggga 3480
ttggctgaga cgaaaaacat attctcaata aaccctttag ggaaataggc caggttttca 3540
ccgtaacacg ccacatcttg cgaatatatg tgtagaaact gccggaaatc gtcgtggtat 3600
tactccaga gcgatgaaaa cgtttcagtt tgctcatgga aaacggtgta acaagggtga 3660
acactatccc atatcaccag ctcaccgtct ttcatcgcca tacggaactc cgggtgagca 3720
ttcatcaggc gggcaagaat gtgaataaag gccggataaa acttgtgctt atttttcttt 3780
acggtcttta aaaaggccgt aatatccagc tgaacggtct gggtataggt acattgagca 3840
actgactgaa atgcctcaaa atgttcttta cgatgccatt gggatatatc aacggtggta 3900
tatccagtga tttttttctc cattttagct tccttagctc ctgaaaatct cgataactca 3960
aaaaatacgc ccggtagtga tcttatttca ttatggtgaa agttggaacc tcacccgacg 4020
tctaattgta gttagctcac tcattaggca cccagggtt tacactttat gcttccggct 4080
cgtatgttgt gtggaattgt gagcggataa caatttcaca caggaaacag ctatgaccat 4140
gattacgaat t 4151

```

<210> 254

<211> 638

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; pMORPH18_Fab protein

<400> 254

```

Met Lys Lys Thr Ala Ile Ala Ile Ala Val Ala Leu Ala Gly Phe Ala
1           5           10           15

```

105/165

Thr Val Ala Gln Ala Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu
 20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
 35 40 45

Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
 50 55 60

Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val
 65 70 75 80

Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 85 90 95

Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
 100 105 110

His Tyr Thr Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
 115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
 130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
 145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
 165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
 180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
 195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
 210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Ala Met Lys Gln Ser
 225 230 235 240

Thr Ile Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr Pro Val Thr Lys
 245 250 255

106/165

Ala Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
 260 265 270

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
 275 280 285

Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
 290 295 300

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
 305 310 315 320

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
 325 330 335

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
 340 345 350

Cys Ala Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly
 355 360 365

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
 370 375 380

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
 385 390 395 400

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 405 410 415

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 420 425 430

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 435 440 445

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 450 455 460

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
 465 470 475 480

Phe Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Lys Met Ala

107/165

485

490

495

Asn Ala Asn Lys Gly Ala Met Thr Glu Asn Ala Asp Glu Asn Ala Leu
 500 505 510

Gln Ser Asp Ala Lys Gly Lys Leu Asp Ser Val Ala Thr Asp Tyr Gly
 515 520 525

Ala Ala Ile Asp Gly Phe Ile Gly Asp Val Ser Gly Leu Ala Asn Gly
 530 535 540

Asn Gly Ala Thr Gly Asp Phe Ala Gly Ser Asn Ser Gln Met Ala Gln
 545 550 555 560

Val Gly Asp Gly Asp Asn Ser Pro Leu Met Asn Asn Phe Arg Gln Tyr
 565 570 575

Leu Pro Ser Leu Pro Gln Ser Val Glu Cys Arg Pro Phe Val Phe Gly
 580 585 590

Ala Gly Lys Pro Tyr Glu Phe Ser Ile Asp Cys Asp Lys Ile Asn Leu
 595 600 605

Phe Arg Gly Val Phe Ala Phe Leu Leu Tyr Val Ala Thr Phe Met Tyr
 610 615 620

Val Phe Ser Thr Phe Ala Asn Ile Leu Arg Asn Lys Glu Ser
 625 630 635

<210> 255
 <211> 5020
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; pMORPH x9

<400> 255
 atcgtgctga cccagccgcc ttcagtgagt ggcgccaccag gtcagcgtgt gaccatctcg 60
 tgtagcggca gcagcagcaa cattggcagc aactatgtga gctggtacca gcagttgccc 120
 gggacggcgc cgaaactgct gatttatgat aacaaccagc gtccctcagg cgtgccggat 180
 cgttttagcg gatccaaaag cggcaccagc gcgagccttg cgattacggg cctgcaaagc 240
 gaagacgaag cggattatta ttgccagagc tatgacatgc ctcaggctgt gtttggcggc 300
 ggcacgaagt ttaaccgttc ttggccagcc gaaagccgca ccgagtgtga cgctgtttcc 360

108/165

gccgagcagc	gaagaattgc	aggcgaacaa	agcgaccctg	gtgtgcctga	ttagcgactt	420
ttatccggga	gccgtgacag	tggcctggaa	ggcagatagc	agccccgtca	aggcgggagt	480
ggagaccacc	acaccctcca	aacaaagcaa	caacaagtac	gcggccagca	gctatctgag	540
cctgacgcct	gagcagtgga	agtcccacag	aagctacagc	tgccagggtca	cgcatgaggg	600
gagcaccgtg	gaaaaaaccg	ttgcgccgac	tgaggcctga	taagcatgcg	taggagaaaa	660
taaaatgaaa	caaagcacta	ttgcaactggc	actcttaccg	ttgctcttca	cccctgttac	720
caaagcccag	gtgcaattga	aagaaagcgg	cccgccctg	gtgaaaccga	cccaaaccct	780
gaccctgacc	tgtacctttt	cgggatttag	cctgtccacg	tctggcgttg	gcgtgggctg	840
gattcgccag	ccgcctggga	aagccctcga	gtggctggct	ctgattgatt	gggatgatga	900
taagtattat	agcaccagcc	tgaaaacgcg	tctgaccatt	agcaaagata	cttcgaaaaa	960
tcagggtggtg	ctgactatga	ccaacatgga	cccggtggat	acggccacct	attattgcgc	1020
gcgttctcct	cgttatcgtg	gtgcttttga	ttattggggc	caaggcaccc	tggtgacggt	1080
tagctcagcg	tcgaccaaag	gtccaagcgt	gtttccgctg	gctccgagca	gcaaaagcac	1140
cagcggcggc	acggctgccc	tgggctgcct	ggttaaagat	tatttcccgg	aaccagtcac	1200
cgtgagctgg	aacagcgggg	cgctgaccag	cggcgtgcat	acctttccgg	cggtgctgca	1260
aagcagcggc	ctgtatagcc	tgagcagcgt	tgtgaccgtg	ccgagcagca	gcttaggcac	1320
tcagacctat	atltgcaacg	tgaaccataa	accgagcaac	accaaagtgg	ataaaaaagt	1380
ggaaccgaaa	agcgaattcg	actataaaga	tgacgatgac	aaaggcgcgc	cgtggagcca	1440
cccgcagtth	gaaaaatgat	aagcttgacc	tgtgaagtga	aaaatggcgc	agattgtgcg	1500
acattttttt	tgtctgccgt	ttaattaaag	gggggggggg	gccggcctgg	gggggggtgt	1560
acatgaaatt	gtaaacgtta	atatthttgt	aaaattcgcg	ttaaattttt	gttaaattcag	1620
ctcatttttt	aaccaatagg	ccgaaatcgg	caaaatccct	tataaatcaa	aagaatagac	1680
cgagataggg	ttgagtgttg	ttccagtttg	gaacaagagt	ccactattaa	agaacgtgga	1740
ctccaacgtc	aaagggcgaa	aaaccgtcta	tcagggcgat	ggcccactac	gagaaccatc	1800
accctaatac	agthtttttg	ggtcgaggtg	ccgtaaagca	ctaaatcgga	accctaaagg	1860
gagccccoga	tttagagctt	gacggggaaa	gccggcgaa	gtggcgagaa	aggaagggaa	1920
gaaagcgaaa	ggagcggggc	ctagggcgct	ggcaagtgtg	gcggtcacgc	tgcgcgtaac	1980
caccacaccc	gccgcgctta	atgcgccgct	acagggcgcg	tgctagacta	gtgttttaaac	2040
cggaccgggg	gggggcttaa	gtgggctgca	aaacaaaacg	gcctcctgtc	aggaagccgc	2100

109/165

ttttatcggg tagcctcact gcccgccttc cagtcgggaa acctgtcgtg ccagctgcat	2160
cagtgaatcg gccaacgcgc ggggagaggc ggtttgcgta ttgggagcca gggtaggttt	2220
tcttttcacc agtgagacgg gcaacagctg attgcccttc accgcctggc cctgagagag	2280
ttgcagcaag cgggtccacgc tggtttgccc cagcaggcga aaatcctggt tgatgggtgt	2340
cagcggcggg atataacatg agctgtcctc ggtatcgtcg tatccacta ccgagatgtc	2400
cgcaccaacg cgcagcccgg actcggtaat ggcacgcatt gcgcccagcg ccatctgac	2460
gttggcaacc agcatcgcag tgggaacgat gccctcattc agcatttgca tggtttggtg	2520
aaaaccggac atggcactcc agtcgccttc ccgttcgcgt atcggctgaa tttgattgcg	2580
agtgagatat ttatgccagc cagccagacg cagacgcgcc gagacagaac ttaatgggcc	2640
agctaacagc gcgatttgct ggtggcccaa tgcgaccaga tgctccacgc ccagtcgcgt	2700
accgtcctca tgggagaaaa taatactgtt gatgggtgtc tggtcagaga catcaagaaa	2760
taacgccgga acattagtgc aggcagett cacagcaata gcatacctggt catccagcgg	2820
atagttaata atcagcccac tgacacgttg cgcgagaaga ttgtgcaccg ccgctttaca	2880
ggcttcgacg ccgcttcggt ctaccatcga cagcaccag ctggcaccga gttgatcggc	2940
gcgagattta atcgcgcgca caatttgca cggcgcgtgc agggccagac tggaggtggc	3000
aacgccaatc agcaacgact gtttgccgc cagttgttgt gccacgcggt taggaatgta	3060
attcagctcc gccatgcgcg cttccacttt ttcccgcgtt ttgcgagaaa cgtggctggc	3120
ctggttcacc acgcgggaaa cggcttgata agagacaccg gcatactctg cgacatcgta	3180
taacgttact ggtttcacat tcaccaccct gaattgactc tcttcggggc gctatcatgc	3240
cataccgcga aagggttttg gccattcgat gctagccatg tgagcaaaag gccagcaaaa	3300
ggccaggaac cgtaaaaagg ccgcgttgct ggcgtttttc cataggctcc gccccctga	3360
cgagcatcac aaaaatcgac gctcaagtca gaggtggcga aaccgcagag gactataaag	3420
ataccaggcg tttccccctg gaagctccct cgtgcgcctc cctgttcgga ccctgccgct	3480
taccggatac ctgtccgcct ttctcccttc gggaagcgtg gcgctttctc atagctcacg	3540
ctgtaggtat ctcagttcgg tgtaggctgt tcgctccaag ctgggctgtg tgcacgaacc	3600
ccccgttcag ccgcaccgct gcgccttata cggtaactat cgtcttgagt ccaaccgggt	3660
aagacacgac ttatcgccac tggcagcagc cactggtaac aggattagca gagcgaggta	3720
tgtaggcgggt gctacagagt tcttgaagtg gtggcctaac tacggctaca ctagaagaac	3780
agtatttggt atctgcgctc tgctgtagcc agttaccttc ggaaaaagag ttggtagctc	3840
ttgatccggc aaacaaacca ccgctggtag cggtaggttt tttgtttgca agcagcagat	3900

110/165

```

tacgcgacaga aaaaaaggat ctcaagaaga tcctttgatc ttttctacgg ggtctgacgc 3960
tcagtggaaac gaaaactcac gttaagggat tttggtcaga tctagcacca ggcgtttaag 4020
ggcaccaata actgccttaa aaaaattacg ccccgccctg ccactcatcg cagtactgtt 4080
gtaattcatt aagcattctg ccgacatgga agccatcaca aacggcatga tgaacctgaa 4140
tcgccagcgg catcagcacc ttgtgcctt gcgtataata tttgcccata gtgaaaacgg 4200
gggcgaagaa gttgtccata ttggctacgt ttaaatacaa actggtgaaa ctcacccagg 4260
gattggctga gacgaaaaac atattctcaa taaacccttt agggaaatag gccaggtttt 4320
cacgtaaca cgccacatct tgcgaatata tgtgtagaaa ctgccggaaa tcgtcgtggt 4380
attcactcca gagcgatgaa aacgtttcag tttgctcatg gaaaacgggtg taacaagggt 4440
gaacactatc ccatatcacc agctcacctg ctttcattgc catacggaac tccgggtgag 4500
cattcatcag gcgggcaaga atgtgaataa aggccggata aaacttgtgc ttatTTTTTct 4560
ttacggtctt taaaaaggcc gtaatatcca gctgaacgggt ctgggttatag gtacattgag 4620
caactgactg aaatgcctca aaatgttctt tacgatgcca ttgggatata tcaacgggtg 4680
tatatccagt gatTTTTTtcc tccatttttag cttccttagc tcctgaaaat ctcgataact 4740
caaaaaatac gcccggtagt gatcttattt cattatgggtg aaagttggaa cctcaccgga 4800
cgtctaattgt gagttagctc actcattagg caccocaggc tttacacttt atgcttccgg 4860
ctcgtatggt gtgtggaatt gtgagcggat aacaatttca cacaggaaac agctatgacc 4920
atgattacga atttctagat aacgagggca aaaaatgaaa aagacagcta tcgcgattgc 4980
agtggcactg gctgggtttcg ctaccgtagc gcaggccgat 5020

```

```

<210> 256
<211> 7
<212> PRT
<213> artificial sequence

```

```

<220>
<223> synthetic construct

```

```

<400> 256

```

```

Ala Glu Phe Arg His Asp Cys
1          5

```

```

<210> 257
<211> 7
<212> PRT
<213> artificial sequence

```

111/165

<220>

<223> synthetic construct

<400> 257

Glu Phe Arg His Asp Ser Cys
1 5

<210> 258

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 258

Phe Arg His Asp Ser Gly Cys
1 5

<210> 259

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 259

Arg His Asp Ser Gly Tyr Cys
1 5

<210> 260

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 260

His Asp Ser Gly Tyr Glu Cys
1 5

<210> 261

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

112/165

<400> 261

Asp Ser Gly Tyr Glu Val Cys
1 5

<210> 262

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 262

Ser Gly Tyr Glu Val His Cys
1 5

<210> 263

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 263

Tyr Glu Val His His Gln Cys
1 5

<210> 264

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 264

Glu Val His His Gln Lys Cys
1 5

<210> 265

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 265

Val His His Gln Lys Leu Cys

113/165

1

5

<210> 266
<211> 7
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 266

His His Gln Lys Leu Val Cys
1 5

<210> 267
<211> 7
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 267

His Gln Lys Leu Val Phe Cys
1 5

<210> 268
<211> 7
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 268

Gln Lys Leu Val Phe Phe Cys
1 5

<210> 269
<211> 7
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 269

Lys Leu Val Phe Phe Ala Cys
1 5

114/165

<210> 270
<211> 7
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 270

Leu Val Phe Phe Ala Glu Cys
1 5

<210> 271
<211> 7
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 271

Val Phe Phe Ala Glu Asp Cys
1 5

<210> 272
<211> 7
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 272

Phe Phe Ala Glu Asp Val Cys
1 5

<210> 273
<211> 7
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 273

Phe Ala Glu Asp Val Gly Cys
1 5

<210> 274
<211> 7
<212> PRT

115/165

<213> artificial sequence

<220>

<223> synthetic construct

<400> 274

Ala Glu Asp Val Gly Ser Cys
1 5

<210> 275

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 275

Glu Asp Val Gly Ser Asn Cys
1 5

<210> 276

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 276

Asp Val Gly Ser Asn Lys Cys
1 5

<210> 277

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 277

Val Gly Ser Asn Lys Gly Cys
1 5

<210> 278

<211> 7

<212> PRT

<213> artificial sequence

<220>

116/165

<223> synthetic construct

<400> 278

Gly Ser Asn Lys Gly Ala Cys
1 5

<210> 279

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 279

Cys Ser Asn Lys Gly Ala Ile
1 5

<210> 280

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 280

Cys Asn Lys Gly Ala Ile Ile
1 5

<210> 281

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 281

Cys Lys Gly Ala Ile Ile Gly
1 5

<210> 282

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 282

117/165

Cys Gly Leu Met Val Gly Gly
1 5

<210> 283
<211> 7
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 283

Cys Met Val Gly Gly Val Val
1 5

<210> 284
<211> 7
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 284

Cys Gly Gly Val Val Ile Ala
1 5

<210> 285
<211> 6
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; peptide 1 A beta

<400> 285

Ala Glu Phe Arg His Asp
1 5

<210> 286
<211> 7
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; peptide 2 A beta

<400> 286

Glu Phe Arg His Asp Ser Gly
1 5

118/165

<210> 287
<211> 5
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; peptide 3 A beta

<400> 287

Glu Phe Arg His Asp
1 5

<210> 288
<211> 4
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; peptide 4 A beta

<400> 288

His Asp Ser Gly
1

<210> 289
<211> 5
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; peptide 5 A beta

<400> 289

His His Gln Lys Leu
1 5

<210> 290
<211> 6
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; peptide 6 A beta

<400> 290

Leu Val Phe Phe Ala Glu
1 5

<210> 291

119/165

<211> 6
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; peptide 7 A beta

<400> 291

Val Phe Phe Ala Glu Asp
1 5

<210> 292
<211> 4
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; peptide 8 A beta

<400> 292

Val Phe Phe Ala
1

<210> 293
<211> 6
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; peptide 9 A beta

<400> 293

Phe Phe Ala Glu Asp Val
1 5

<210> 294
<211> 360
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 294
caattggtgg aaagcggcgg cggcctggtg caaccgggcg gcagcctgcg tctgagctgc 60
gcggcctccg gatttacctt tagcagctat gcgatgagct ggggtgcgcca agcccctggg 120
aaggggtctcg agtgggtgag cgttatttct gagaagtctc gttttattta ttatgctgat 180
tctgttaagg gtcgtttttac catttcacgt gataattcga aaaacaccct gtatctgcaa 240
atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtct tactcattat 300

120/165

gctcgttatt atcgttattt tgatgtttgg ggccaaggca ccctggtgac ggtagctca 360

<210> 295
 <211> 120
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 295

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
 1 5 10 15

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
 20 25 30

Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Val
 35 40 45

Ile Ser Glu Lys Ser Arg Phe Ile Tyr Tyr Ala Asp Ser Val Lys Gly
 50 55 60

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
 65 70 75 80

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
 85 90 95

Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val Trp Gly Gln
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 296
 <211> 360
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 296

caattggtgg aaagcggcgg cggcctggtg caaccggggcg gcagcctgcg tctgagctgc 60

gcggcctccg gatttacctt tagcagctat gcgatgagct ggggtgcgcca agcccctggg 120

121/165

```

aaggggtctcg agtgggtgag cgctatttct gagacttcta ttcgtaagta ttatgctgat      180
tctgttaagg gtcgtttttac catttcaogt gataattcga aaaacaccct gtatctgcaa      240
atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtct tactcattat      300
gctcgttatt atcgttattt tgatgtttgg ggccaaggca ccctggtgac ggtagctca      360

```

<210> 297
 <211> 120
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 297

```

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
1              5              10              15

```

```

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
              20              25              30

```

```

Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala
              35              40              45

```

```

Ile Ser Glu Thr Ser Ile Arg Lys Tyr Tyr Ala Asp Ser Val Lys Gly
50              55              60

```

```

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
65              70              75              80

```

```

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
              85              90              95

```

```

Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val Trp Gly Gln
100              105              110

```

```

Gly Thr Leu Val Thr Val Ser Ser
115              120

```

<210> 298
 <211> 360
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

122/165

```

<400> 298
caattggtgg aaagcggcgg cggcctggtg caaccgggcg gcagcctgcg tctgagctgc      60
gcggcctccg gatttacctt tagcagctat gcgatgagct gggcgcgcca agcccctggg      120
aagggtctcg agtgggtgag cggtatttct cagactggtc gtaagattta ttatgctgat      180
tctgttaagg gtcgttttac catttcacgt gataattcga aaaacaccct gtatctgcaa      240
atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtct tactcattat      300
gctcgttatt atcggttatt tgatgtttgg ggccaaggca ccttggtgac ggtagctca      360

```

```

<210> 299
<211> 120
<212> PRT
<213> artificial sequence

```

```

<220>
<223> synthetic construct

```

```

<400> 299

```

```

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
1           5           10           15

```

```

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
          20           25           30

```

```

Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Val
35           40           45

```

```

Ile Ser Gln Thr Gly Arg Lys Ile Tyr Tyr Ala Asp Ser Val Lys Gly
50           55           60

```

```

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
65           70           75           80

```

```

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
          85           90           95

```

```

Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val Trp Gly Gln
100           105           110

```

```

Gly Thr Leu Val Thr Val Ser Ser
115           120

```

```

<210> 300
<211> 360
<212> DNA

```

123/165

<213> artificial sequence

<220>

<223> synthetic construct

<400> 300

```

caattggtgg aaagcggcgg cggcctggtg caaccgggcg gcagcctgcg tctgagctgc      60
gcggcctccg gatttacctt tagcagctat gcgatgagct gggcgcgcca agcccctggg      120
aagggctctcg agtgggtgag cgttatttct cagactggtc gtaagattta ttatgctgat      180
tctgttaagg gtcgttttac catttcacgt gataattcga aaaacaccct gtatctgcaa      240
atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtct tactcattat      300
gctcgttatt atcgttatatt tgatgtttgg ggccaaggca ccctgggtgac ggtagctca      360

```

<210> 301

<211> 120

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 301

```

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
1             5             10             15

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
                20             25             30

Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Val
35             40             45

Ile Ser Gln Thr Gly Arg Lys Ile Tyr Tyr Ala Asp Ser Val Lys Gly
50             55             60

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
65             70             75             80

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
                85             90             95

Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val Trp Gly Gln
                100            105            110

Gly Thr Leu Val Thr Val Ser Ser
115             120

```

124/165

<210> 302
 <211> 360
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 302
 caattggtgg aaagcggcgg cggcctggtg caaccgggcg gcagcctgcg tctgagctgc 60
 gcggcctccg gatttacctt tagcagctat gcgatgagct ggggtgcgcca agcccctggg 120
 aaggggtctcg agtgggtgag cgttatttct gagactggta agaataattta ttatgctgat 180
 tctgttaagg gtcgttttac catttcacgt gataattcga aaaacaccct gtatctgcaa 240
 atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtct tactcattat 300
 gctcgttatt atcgttattt tgatgtttgg ggccaaggca ccctggtgac ggtagctca 360

<210> 303
 <211> 120
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 303

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
 1 5 10 15

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
 20 25 30

Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Val
 35 40 45

Ile Ser Glu Thr Gly Lys Asn Ile Tyr Tyr Ala Asp Ser Val Lys Gly
 50 55 60

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
 65 70 75 80

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
 85 90 95

Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val Trp Gly Gln

125/165

100

105

110

Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 304
 <211> 360
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 304
 caattggtgg aaagcggcgg cggcctggtg caaccgggcg gcagcctgcg tctgagctgc 60
 gcggcctccg gatttacctt tagcagctat gcgatgagct gggcgcgcca agcccctggg 120
 aagggtctcg agtgggtgag cgttatttct gagactggta agaatatatta ttatgctgat 180
 tctgttaagg gtcgttttac catttcacgt gataattcga aaaacaccct gtatctgcaa 240
 atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtct tactcattat 300
 gctcgttatt atcgttattt tgatgtttgg ggccaaggca ccctggtgac ggtagctca 360

<210> 305
 <211> 120
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 305

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
 1 5 10 15

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
 20 25 30

Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Val
 35 40 45

Ile Ser Glu Thr Gly Lys Asn Ile Tyr Tyr Ala Asp Ser Val Lys Gly
 50 55 60

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
 65 70 75 80

126/165

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
85 90 95

Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

```
<210> 306
<211> 360
<212> DNA
<213> artificial sequence
```

```
<220>
<223> synthetic construct
```

[illegible]

```
<210> 307
<211> 120
<212> PRT
<213> artificial sequence
```

```
<220>
<223> synthetic construct
```

<400> 307

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
1 5 10 15

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
20 25 30

Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala
35 40 45

Ile Ser Glu Ser Gly Lys Thr Lys Tyr Tyr Ala Asp Ser Val Lys Gly
50 55 60

127/165

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
65 70 75 80

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
85 90 95

Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 308
<211> 372
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 308
caattggtgg aaagcggcgg cggcctggtg caaccgggcg gcagcctgcg tctgagctgc 60
gcggcctccg gatttacctt tagcagctat gcgatgagct ggggtgcgcca agcccctggg 120
aagggtctcg agtgggtgag cgctattaat ggtactggta tgaagaagta ttatgctgat 180
tctgttaagg gtcgtttttac catttcacgt gataattcga aaaacaccct gtatctgcaa 240
atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtgg taagggtaat 300
actcataagc cttatgggta tgttcgttat tttgatgttt ggggcccaagg caccctgggtg 360
acggttagct ca 372

<210> 309
<211> 124
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 309

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
1 5 10 15

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
20 25 30

128/165

Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala
 35 40 45

Ile Asn Gly Thr Gly Met Lys Lys Tyr Tyr Ala Asp Ser Val Lys Gly
 50 55 60

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
 65 70 75 80

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
 85 90 95

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
 100 105 110

Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 310
 <211> 372
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 310
 caattggtgg aaagcggcgg cggcctggtg caaccgggcg gcagcctgcg tctgagctgc 60
 gcggcctccg gatttacctt tagcagctat gcgatgagct gggcgcgcca agcccctggg 120
 aagggtctcg agtgggtgag cgctattaat tataatgggtg ctcgtattta ttatgctgat 180
 tctgttaagg gtcgttttac catttcacgt gataattcga aaaacaccct gtatctgcaa 240
 atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtgg taagggtaat 300
 actcataagc cttatgggta tggttcgttat tttgatgttt ggggccaagg caccctggtg 360
 acggtttagct ca 372

<210> 311
 <211> 124
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 311

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu

129/165

1				5					10					15	
Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr	Ala	Met
			20					25					30		
Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	Ser	Ala
		35					40					45			
Ile	Asn	Tyr	Asn	Gly	Ala	Arg	Ile	Tyr	Tyr	Ala	Asp	Ser	Val	Lys	Gly
	50					55					60				
Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr	Leu	Gln
65					70					75					80
Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala	Arg
				85					90					95	
Gly	Lys	Gly	Asn	Thr	His	Lys	Pro	Tyr	Gly	Tyr	Val	Arg	Tyr	Phe	Asp
			100					105					110		
Val	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser				
		115					120								

<210>	312
<211>	372
<212>	DNA
<213>	artificial sequence

```
<220>
<223> synthetic construct
```

<400>	312								
caattggttg	aaagcggcg	cggcctggtg	caaccgggcg	gcagcctgcg	tctgagctgc				60
gcggcctccg	gatttacctt	tagcagctat	gcgatgagct	gggtgcgcc	agcccctggg				120
aagggtctcg	agtgggtgag	cgctattaat	gctgatggta	atcgtaahta	ttatgctgat				180
tctgttaagg	gtcgttttac	catttcacgt	gataattcga	aaaacaccct	gtatctgcaa				240
atgaacagcc	tgcgtgcgga	agatacggcc	gtgtattatt	gcgcgcgtgg	taagggtaat				300
actcataagc	cttatggta	tgttcgttat	tttgatgttt	ggggccaagg	caccctgggtg				360
acggttagct	ca								372

```
<210> 313
<211> 124
<212> PRT
<213> artificial sequence
```


130/165

<220>

<223> synthetic construct

<400> 313

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
 1 5 10 15

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
 20 25 30

Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala
 35 40 45

Ile Asn Ala Asp Gly Asn Arg Lys Tyr Tyr Ala Asp Ser Val Lys Gly
 50 55 60

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
 65 70 75 80

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
 85 90 95

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
 100 105 110

Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 314

<211> 372

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 314

caattggtgg aaagcggcgg cggcctggtg caaccgggcg gcagcctgcg tctgagctgc 60

gcggcctccg gatttacctt tagcagctat gcgatgagct ggggtgcgcca agcccctggg 120

aaaggtctcg agtgggtgag cgctattaat gctgatggta atcgtaagta ttatgctgat 180

tctgttaagg gtcgttttac catttcacgt gataattcga aaaacaccct gtatctgcaa 240

atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtgg taagggtaat 300

actcataagc cttatgggta tgttcgttat tttgatgttt ggggcccaagg caccctggtg 360

131/165

acggtttagct ca

372

<210> 315
 <211> 124
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 315

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
 1 5 10 15

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
 20 25 30

Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala
 35 40 45

Ile Asn Ala Asp Gly Asn Arg Lys Tyr Tyr Ala Asp Ser Val Lys Gly
 50 55 60

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
 65 70 75 80

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
 85 90 95

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
 100 105 110

Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 316
 <211> 372
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 316
 caattggtgg aaagcggcgg cggcctggtg caaccggggcg gcagcctgcg tctgagctgc 60
 gcggcctccg gatttacctt tagcagctat gcgatgagct ggggtgcgcca agcccctggg 120
 aagggtctcg agtgggtgag cgctattaat gctaattggtt ataagaagta ttatgctgat 180

132/165

```

tctgttaagg gtcgtttttac catttcacgt gataattcga aaaacaccct gtatctgcaa      240
atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtgg taagggtaat      300
actcataagc cttatgggta tgttcggtat tttgatgttt ggggccaaagg caccctgggtg      360
acggttagct ca                                                              372

```

<210> 317
 <211> 124
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 317

```

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
1              5              10              15

```

```

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
              20              25              30

```

```

Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala
35              40              45

```

```

Ile Asn Ala Asn Gly Tyr Lys Lys Tyr Tyr Ala Asp Ser Val Lys Gly
50              55              60

```

```

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
65              70              75              80

```

```

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
              85              90              95

```

```

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
100              105              110

```

```

Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115              120

```

<210> 318
 <211> 372
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

133/165

```

<400> 318
caattggtgg aaagcggcgg cggcctggtg caaccgggcg gcagcctgcg tctgagctgc      60
gcggcctccg gatttacctt tagcagctat gcgatgagct gggcgcgcca agcccctggg      120
aaggggtctcg agtgggtgag cgctattaat gctaattggtt ataagaagta ttatgctgat      180
tctgttaagg gtcgtttttac catttcacgt gataattcga aaaacaccct gtatctgcaa      240
atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtgg taagggtaat      300
actcataagc cttatgggta tggttcgttat tttgatgttt ggggcccaagg caccctggtg      360
acggtttagct ca                                                                372

```

```

<210> 319
<211> 124
<212> PRT
<213> artificial sequence

```

```

<220>
<223> synthetic construct

```

```

<400> 319

```

```

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
1           5           10           15

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
          20           25           30

Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala
          35           40           45

Ile Asn Ala Asn Gly Tyr Lys Lys Tyr Tyr Ala Asp Ser Val Lys Gly
          50           55           60

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
65           70           75           80

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
          85           90           95

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
          100          105          110

Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
          115          120

```

134/165

<210> 320
 <211> 372
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 320
 caattggtgg aaagcggcgg cggcctggtg caaccgggcg gcagcctgcg tctgagctgc 60
 gcggcctccg gatttacctt tagcagctat gcgatgagct gggcgcgcca agcccctggg 120
 aaggggtctcg agtgggtgag cgctattaat gctaattggtt ataagaagta ttatgctgat 180
 tctgttaagg gtcgttttac catttcacgt gataattcga aaaacaccct gtatctgcaa 240
 atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtgg taagggtaat 300
 actcataagc cttatgggta tggtcgttat tttgatgttt ggggccaagg caccctggtg 360
 acggtttagct ca 372

<210> 321
 <211> 124
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 321

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
 1 5 10 15

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
 20 25 30

Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala
 35 40 45

Ile Asn Ala Asn Gly Tyr Lys Lys Tyr Tyr Ala Asp Ser Val Lys Gly
 50 55 60

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
 65 70 75 80

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
 85 90 95

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp

135/165

100

105

110

Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 322
 <211> 366
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 322
 caattggtgg aaagcggcgg cggcctggtg caacogggcg gcagcctgcg tctgagctgc 60
 ggggcctccg gatttacctt tagcagctat gcgatgagct gggcgcgcca agcccctggg 120
 aagggtctcg agtgggtgag cgtatatttct cgttctggtt ctaatattta ttatgctgat 180
 tctgttaagg gtcgtttttac catttcacgt gataattcga aaaacaccct gtatctgcaa 240
 atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtct tctttctcgt 300
 gggtataatg gttattatca taagtttgat gtttggggcc aaggcaccct ggtgacgggt 360
 agctca 366

<210> 323
 <211> 122
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 323

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
 1 5 10 15

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
 20 25 30

Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala
 35 40 45

Ile Ser Arg Ser Gly Ser Asn Ile Tyr Tyr Ala Asp Ser Val Lys Gly
 50 55 60

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
 65 70 75 80

136/165

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
 85 90 95

Leu Leu Ser Arg Gly Tyr Asn Gly Tyr Tyr His Lys Phe Asp Val Trp
 100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 324
 <211> 330
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 324
 gatatcgtgc tgaccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc 60
 ctgagctgca gagcgagccg gcgattcat gtttattatc tggcgtggta ccagcagaaa 120
 ccagggtcaag caccgcgtct attaatattat ggcgcgagca gccgtgcaac tgggggtcccg 180
 gcgcgttttta gcggctcttg atccggcacg gattttaccc tgaccattag cagcctggaa 240
 cctgaagact ttgcgactta ttattgccag cagacttatg attatcctcc tacctttggc 300
 cagggtacga aagttgaaat taaacgtacg 330

<210> 325
 <211> 110
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 325

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Arg Arg Ile His Val Tyr
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser

137/165

50

55

60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
 65 70 75 80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Tyr Asp Tyr Pro
 85 90 95

Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
 100 105 110

<210> 326
 <211> 330
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 326
 gatatcgtgc tgaccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc 60
 ctgagctgca gagcgagccg gcgtattcat gtttattatc tggcgtggta ccagcagaaa 120
 ccagggtcaag caccgctctc attaatattat ggcgcgagca gccgtgcaac tgggggtcccg 180
 gcgcgtttta gcggctcttg atccggcacg gattttaccc tgaccattag cagcctggaa 240
 cctgaagact ttgcgactta ttattgccag cagaattatg attatcctcc tacctttggc 300
 cagggtacga aagttgaaat taaacgtacg 330

<210> 327
 <211> 110
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 327

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Arg Arg Ile His Val Tyr
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

138/165

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
 50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
 65 70 75 80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Tyr Asp Tyr Pro
 85 90 95

Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
 100 105 110

<210> 328
 <211> 330
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 328
 gatatcgtgc tgaccagag cccggcgacc ctgagcctgt ctccgggcca acgtgcgacc 60
 ctgagctgca gagcgagcca gcgtcttggt cgtctttatc tggcgtggta ccagcagaaa 120
 ccagggtcaag caccgcgtct attaatattat ggcgcgagca gccgtgcaac tgggggtcccg 180
 ggcggtttta gcggctctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240
 cctgaagact ttgcgactta ttattgccag cagaattatg attatcctcc tacctttggc 300
 cagggtacga aagttgaaat taaacgtacg 330

<210> 329
 <211> 110
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 329

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Leu Gly Arg Leu
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

139/165

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
 50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
 65 70 75 80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Tyr Asp Tyr Pro
 85 90 95

Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
 100 105 110

<210> 330
 <211> 330
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 330
 gatatcgtgc tgaccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc 60
 ctgagctgca gagcgagccg gcgtattcat gtttattatc tggcgtggta ccagcagaaa 120
 ccagggtcaag caccgcgtct attaatattat ggcgcgagca gccgtgcaac tgggggtccc 180
 gcgcgtttta gcggctctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240
 cctgaagact ttgcgactta ttattgccag cagacttatg attatcctcc tacctttggc 300
 cagggtagca aagttgaaat taaacgtacg 330

<210> 331
 <211> 110
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 331

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Arg Arg Ile His Val Tyr
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

140/165

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
 50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
 65 70 75 80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Tyr Asp Tyr Pro
 85 90 95

Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
 100 105 110

<210> 332
 <211> 330
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 332
 gatatacgtgc tgaccagag cccggcgacc ctgagcctgt ctccgggcga acgtgacgacc 60
 ctgagctgca gagcgagccg gcgtattcat gtttattatc tggcgtggta ccagcagaaa 120
 ccagggtcaag caccgcgtct attaatattat ggcgcgagca gccgtgcaac tgggggtcccg 180
 gcgcgttttta gcggctctgg atccggcgcg gattttaccc tgaccattag cagcctggaa 240
 cctgaagact ttgcgactta ttattgccag cagacttatg attatcctcc tacctttggc 300
 cagggtacga aagttgaaat taaacgtacg 330

<210> 333
 <211> 110
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 333

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Arg Arg Ile His Val Tyr
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu

141/165

35

40

45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
 50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
 65 70 75 80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Tyr Asp Tyr Pro
 85 90 95

Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
 100 105 110

<210> 334
 <211> 330
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 334
 gatatcgtgc tgaccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc 60
 ctgagctgca gagcgagcca gcgctcttggc cgtctttatc tggcgtggta ccagcagaaa 120
 ccagggtcaag caccgcgtct attaatattat ggcgcgagca gccgtgcaac tgggggtcccg 180
 gcgcggtttta gcggctctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240
 cctgaagact ttgcgactta ttattgccag cagacttatg attatcctcc tacctttggc 300
 cagggtacga aagttgaaat taaacgtacg 330

<210> 335
 <211> 110
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 335

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Leu Gly Arg Leu
 20 25 30

142/165

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
 50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
 65 70 75 80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Tyr Asp Tyr Pro
 85 90 95

Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
 100 105 110

<210> 336
 <211> 330
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 336
 gatatcgtgc tgaccagag cccggcgacc ctgagcctgt ctccggggcga acgtgcgacc 60
 ctgagctgca gagcgagcca gtttattcag cgttttttatc tggcgtggta ccagcagaaa 120
 ccagggtcaag caccgctct attaatattat ggcgcgagca gccgtgcaac tgggggtcccg 180
 gcgcgtttta gcggctctgg atccggcacg gatttttacc tgaccattag cagcctggaa 240
 cctgaagact ttgcggttta ttattgccag cagaattata attatcctcc tacctttggc 300
 cagggtacga aagttgaaat taaacgtacg 330

<210> 337
 <211> 110
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 337

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Phe Ile Gln Arg Phe
 20 25 30

143/165

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Thr Tyr Asn Tyr Pro
85 90 95

Pro	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg	Thr
			100					105					110

```
<210> 338
<211> 330
<212> DNA
<213> artificial sequence
```

```
<220>
<223> synthetic construct
```

<400>	338						
gatatcgtgc	tgacccagag	cccggcgacc	ctgagcctgt	ctccggggcga	acgtgcgacc	60	
ctgagctgca	gagcgagcca	gtatgttgat	cgtacttatc	tggcgtggta	ccagcagaaa	120	
ccagggtcaag	caccgcgtct	attaatttat	ggcgcgagca	gccgtgcaac	tgggggtcccg	180	
gcgcgttttta	gcggctcttg	atccggcacg	gattttaccc	tgaccattag	cagcctggaa	240	
cctgaagact	ttgcgactta	ttattgccag	cagatttatt	cttttcctca	tacctttggc	300	
cagggtacga	aagttgaaat	taaacgtacg				330	

```
<210> 339
<211> 110
<212> PRT
<213> artificial sequence
```

```
<220>
<223> synthetic construct
```

<400> 339

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Tyr Val Asp Arg Thr
20 25 30

144/165

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
 50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
 65 70 75 80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ile Tyr Ser Phe Pro
 85 90 95

His Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
 100 105 110

<210> 340

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 340

gatatcgtgc tgaccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc 60
 ctgagctgca gagcgagcca gcgttttttt tataagtatc tggcgtggta ccagcagaaa 120
 ccagggtcaag caccgcgtct attaatcttct gggttcttcta accgtgcaac tgggggtcccg 180
 gcgcgttttta gcggctctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240
 cctgaagact ttgcggttta ttattgcctt cagctttata atattcctaa tacctttggc 300
 cagggtacga aagttgaaat taaacgtacg 330

<210> 341

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 341

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Phe Phe Tyr Lys

145/165

20

25

30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Ile Ser Gly Ser Ser Asn Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
 50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
 65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Leu Tyr Asn Ile Pro
 85 90 95

Asn Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
 100 105 110

<210> 342
 <211> 330
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 342
 gatatacgtgc tgacccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc 60
 ctgagctgca gagcgagcca gtatgttgat cgtacttatac tggcgtggta ccagcagaaa 120
 ccagggtcaag caccgcgtct attaatattat ggcgcgagca gccgtgcaac tgggggtcccg 180
 gcgcgtttta gcggctctgg atccggcaag gattttaccc tgaccattag cagcctggaa 240
 cctgaagact ttgcgactta ttattgccag cagatttatt cttttcctca tacctttggc 300
 caggggtacga aagttgaaat taaacgtacg 330

<210> 343
 <211> 110
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 343

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Tyr Val Asp Arg Thr
20 25 30

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ile Tyr Ser Phe Pro
85 90 95

His Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

```
<210> 344
<211> 330
<212> DNA
<213> artificial sequence
```

```
<220>
<223> synthetic construct
```

<400>	344								
gatatcgtgc	tgacccagag	cccggcgacc	ctgagcctgt	ctccggggcga	acgtgcgacc				60
ctgagctgca	gagcgagcca	gtatgttttt	cgtcgttatc	tggcgtggta	ccagcagaaa				120
ccagggtcaag	caccgcgtct	attaattttct	ggttctttcta	accgtgcaac	tgggggtcccg				180
gcgcgtttta	gcggtctctgg	atccggcacg	gattttaccc	tgaccattag	cagcctggaa				240
cctgaagact	ttgcggttta	ttattgcctt	cagctttata	atattcctaa	tacctttggc				300
cagggtacga	aagttgaaat	taaacgtacg							330

```
<210> 345
<211> 110
<212> PRT
<213> artificial sequence
```

```
<220>
<223> synthetic construct
```

<400> 345

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

147/165

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Tyr Val Phe Arg Arg
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Ile Ser Gly Ser Ser Asn Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
 50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
 65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Leu Tyr Asn Ile Pro
 85 90 95

Asn Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
 100 105 110

<210> 346
 <211> 330
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 346
 gatatcgtgc tgaccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc 60
 ctgagctgca gagcgagcca gtatgttgat cgtacttatac tggcgtggta ccagcagaaa 120
 ccagggtcaag caccgcgtct attaatattat ggcgcgagca gccgtgcaac tgggggtcccg 180
 ggcgcgtttta gcggctctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240
 cctgaagact ttgcgactta ttattgccag cagatttatt cttttcctca tacctttggc 300
 cagggtacga aagttgaaat taaacgtacg 330

<210> 347
 <211> 110
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 347

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

148/165

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Tyr Val Asp Arg Thr
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ile Tyr Ser Phe Pro
85 90 95

His Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 348
<211> 330
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 348
gatatcgtgc tgaccagag cccggcgacc ctgagcctgt ctccgggcga acgtgogacc 60
ctgagctgca gagcgagcca gcgtctttct cctcgttatc tggcgtggta ccagcagaaa 120
ccaggtcaag caccgcgtct attaatattat ggcgcgagca gccgtgcaac tgggggtcccg 180
gcgcgtttta gcggctctgg atccggcagc gattttaccc tgaccattag cagcctggaa 240
cctgaagact ttgcgactta ttattgcctt cagatttata atatgcctat tacctttggc 300
cagggtacga aagttgaaat taaacgtacg 330

<210> 349
<211> 110
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 349

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly

149/165

1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Leu Ser Pro Arg
 20 25 30
 Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45
 Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
 50 55 60
 Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
 65 70 75 80
 Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Ile Tyr Asn Met Pro
 85 90 95
 Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
 100 105 110

<210> 350
 <211> 330
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 350
 gatatcgtgc tgacccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc 60
 ctgagctgca gagcgagcca gtatgttttt cgtcgttata tggcgtggta ccagcagaaa 120
 ccagggtcaag caccgcgtct attaatcttct gggtcttcta accgtgcaac tgggggtcccg 180
 gcgcgtttta gcggctctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240
 cctgaagact ttgcggttta ttattgcctt cagctttata atattcctaa tacctttggc 300
 cagggtacga aagttgaaat taaacgtacg 330

<210> 351
 <211> 110
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 351

150/165

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Tyr Val Phe Arg Arg
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Ile Ser Gly Ser Ser Asn Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
 50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
 65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Leu Tyr Asn Ile Pro
 85 90 95

Asn Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
 100 105 110

<210> 352
 <211> 330
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 352
 gatatcgtgc tgaccagag cccggcgacc ctgagcctgt ctccgggcca acgtgacgacc 60
 ctgagctgca gagcgagcca gcgtgtttct ggctcgttatc tggcgtggta ccagcagaaa 120
 ccaggtaag caccgcgtct attaatattat ggcgcgagca gccgtgcaac tgggggtcccg 180
 ggcggtttta gcggctctgg atccggcaag gatatttacc tgaccattag cagcctggaa 240
 cctgaagact ttgcgactta ttattgccag cagctttctt cttatcctcc tacctttggc 300
 cagggtacga aagttgaaat taaacgtacg 330

<210> 353
 <211> 110
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 353

151/165

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Val Ser Gly Arg
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
 50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
 65 70 75 80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Ser Ser Tyr Pro
 85 90 95

Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
 100 105 110

<210> 354
 <211> 39
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 354
 cttactcatt atgctcgta ttatcgttat tttgatgtt

39

<210> 355
 <211> 13
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 355

Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val
 1 5 10

<210> 356
 <211> 39
 <212> DNA
 <213> artificial sequence

152/165

<220>

<223> synthetic construct

<400> 356

cttactcatt atgctcgta ttatcggtat tttgatgtt

39

<210> 357

<211> 13

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 357

Leu	Thr	His	Tyr	Ala	Arg	Tyr	Tyr	Arg	Tyr	Phe	Asp	Val
1				5					10			

<210> 358

<211> 39

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 358

cttactcatt atgctcgta ttatcggtat tttgatgtt

39

<210> 359

<211> 13

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 359

Leu	Thr	His	Tyr	Ala	Arg	Tyr	Tyr	Arg	Tyr	Phe	Asp	Val
1				5					10			

<210> 360

<211> 39

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 360

cttactcatt atgctcgta ttatcggtat tttgatgtt

39

153/165

<210> 361
<211> 13
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 361

Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val
1 5 10

<210> 362
<211> 39
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 362

cttactcatt atgctcgta ttatcgttat tttgatgtt

39

<210> 363
<211> 13
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 363

Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val
1 5 10

<210> 364
<211> 39
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 364

cttactcatt atgctcgta ttatcgttat tttgatgtt

39

<210> 365
<211> 13
<212> PRT
<213> artificial sequence

<220>

154/165

<223> synthetic construct

<400> 365

Leu	Thr	His	Tyr	Ala	Arg	Tyr	Tyr	Arg	Tyr	Phe	Asp	Val
1				5					10			

<210> 366

<211> 39

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 366

cttactcatt atgctcgta ttatcggtat tttgatgtt

39

<210> 367

<211> 13

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 367

Leu	Thr	His	Tyr	Ala	Arg	Tyr	Tyr	Arg	Tyr	Phe	Asp	Val
1				5					10			

<210> 368

<211> 51

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 368

ggtaagggtatactcataa gccttatggt tatgttcgtt atttgatgt t

51

<210> 369

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 369

Gly	Lys	Gly	Asn	Thr	His	Lys	Pro	Tyr	Gly	Tyr	Val	Arg	Tyr	Phe	Asp
1				5					10					15	

155/165

Val

<210> 370
<211> 51
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 370
ggtaagggtataactcataa gccttatgggt tatgttcggt attttgatgt t 51

<210> 371
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 371

Gly	Lys	Gly	Asn	Thr	His	Lys	Pro	Tyr	Gly	Tyr	Val	Arg	Tyr	Phe	Asp
1				5					10					15	

Val

<210> 372
<211> 51
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 372
ggtaagggtataactcataa gccttatgggt tatgttcggt attttgatgt t 51

<210> 373
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 373

Gly	Lys	Gly	Asn	Thr	His	Lys	Pro	Tyr	Gly	Tyr	Val	Arg	Tyr	Phe	Asp
1				5					10					15	

156/165

Val

<210> 374
<211> 51
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 374
ggtaagggta atactcataa gccttatggg tatgttcggt attttgatgt t 51

<210> 375
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 375

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
1 5 10 15

Val

<210> 376
<211> 51
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 376
ggtaagggta atactcataa gccttatggg tatgttcggt attttgatgt t 51

<210> 377
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 377

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp

157/165

1 5 10 15

Val

<210> 378
<211> 51
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 378
ggtaagggta atactcataa gccttatggg tatgttcggt attttgatgt t 51

<210> 379
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 379

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
1 5 10 15

Val

<210> 380
<211> 51
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 380
ggtaagggta atactcataa gccttatggg tatgttcggt attttgatgt t 51

<210> 381
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 381

158/165

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
1 5 10 15

Val

<210> 382
<211> 45
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 382
cttctttctc gtggttataa tggttattat cataagtttg atggt 45

<210> 383
<211> 15
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 383

Leu Leu Ser Arg Gly Tyr Asn Gly Tyr Tyr His Lys Phe Asp Val
1 5 10 15

<210> 384
<211> 24
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 384
cagcagactt atgattatcc tcct 24

<210> 385
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 385

Gln Gln Thr Tyr Asp Tyr Pro Pro
1 5

159/165

<210> 386
<211> 24
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 386
cagcagactt atgattatcc tcct

24

<210> 387
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 387

Gln Gln Thr Tyr Asp Tyr Pro Pro
1 5

<210> 388
<211> 24
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 388
cagcagactt atgattatcc tcct

24

<210> 389
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 389

Gln Gln Thr Tyr Asp Tyr Pro Pro
1 5

<210> 390
<211> 24
<212> DNA
<213> artificial sequence

<220>

160/165

<223> synthetic construct

<400> 390
cagcagactt atgattatcc tcct

24

<210> 391
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 391

Gln Gln Thr Tyr Asp Tyr Pro Pro
1 5

<210> 392
<211> 24
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 392
cagcagactt atgattatcc tcct

24

<210> 393
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 393

Gln Gln Thr Tyr Asp Tyr Pro Pro
1 5

<210> 394
<211> 24
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 394
cagcagactt atgattatcc tcct

24

<210> 395

161/165

<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 395

Gln Gln Thr Tyr Asp Tyr Pro Pro
1 5

<210> 396
<211> 24
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 396
cagcagactt ataattatcc tcct

24

<210> 397
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 397

Gln Gln Thr Tyr Asn Tyr Pro Pro
1 5

<210> 398
<211> 24
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 398
cagcagattt attcttttcc tcat

24

<210> 399
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

162/165

<400> 399

Gln Gln Ile Tyr Ser Phe Pro His
1 5

<210> 400

<211> 24

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 400

cttcagcttt ataatattcc taat

24

<210> 401

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 401

Leu Gln Leu Tyr Asn Ile Pro Asn
1 5

<210> 402

<211> 24

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 402

cagcagattt attcttttcc tcat

24

<210> 403

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 403

Gln Gln Ile Tyr Ser Phe Pro His
1 5

<210> 404

163/165

<211> 24
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 404
cttcagcttt ataatattcc taat

24

<210> 405
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 405

Leu Gln Leu Tyr Asn Ile Pro Asn
1 5

<210> 406
<211> 24
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 406
cagcagattt attcttttcc tcat

24

<210> 407
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 407

Gln Gln Ile Tyr Ser Phe Pro His
1 5

<210> 408
<211> 24
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

164/165

<400> 408
cagcagattt attcttttcc tcat

24

<210> 409
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 409

Leu Gln Ile Tyr Asn Met Pro Ile
1 5

<210> 410
<211> 24
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 410
cttcagcttt ataatatcc taat

24

<210> 411
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 411

Leu Gln Leu Tyr Asn Ile Pro Asn
1 5

<210> 412
<211> 24
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 412
cagcagcttt cttcttatcc tect

24

<210> 413
<211> 8
<212> PRT

165/165

<213> artificial sequence

<220>

<223> synthetic construct

<400> 413

Gln Gln Leu Ser Ser Tyr Pro Pro
1 5

<210> 414

<211> 52

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 414

Ile Ser Glu Val Lys Met Asp Ala Glu Phe Arg His Asp Ser Gly Tyr
1 5 10 15

Glu Val His His Gln Lys Leu Val Phe Phe Ala Glu Asp Val Gly Ser
20 25 30

Asn Lys Gly Ala Ile Ile Gly Leu Met Val Gly Gly Val Val Ile Ala
35 40 45

Thr Val Ile Val
50